2. Treatment with pegylated interferon (pegIFN) monotherapy

Effects of treatment with pegIFN monotherapy. There are 11 reports on treatment of dialysis patients using pegIFN monotherapy published by 2009, consisting of nine on pegIFN α-2a and 2 on pegIFN α-2b. The initial administration of pegIFN α-2a was made subcutaneously at 135–180 μg once a week, the SVR rate was 14–75%, and the dropout rate was 0–73% (15–25). Major adverse effects were fever, reduced appetite, malaise, cytopenia, and depression. The dropout rate was low in reports with a high SVR rate but high in those with a low SVR rate.

Comparison of effectiveness between standard IFNα monotherapy and pegIFNα monotherapy. A randomized controlled trial comparing standard IFNα monotherapy and pegIFNα monotherapy has been reported (25). Fifty hemodialysis patients were randomized to pegIFNα-2a and IFNα-2a therapies, the administration of pegIFNα-2a at 135 μg/week and IFNα-2a at 3 MU×3/week was continued for 24 weeks, and the results were evaluated by an intention-to-treat (ITT) analysis. In the pegIFNα-2a and IFNα-2a groups, the SVR rate was 48% and 20% ($P = 0.07$), fever was observed in 12% and 44% ($P = 0.03$), and dropout rate was 0% and 20% ($P = 0.04$), respectively, showing that pegIFN α-2a was more effective and less frequently caused adverse effects than the conventional preparation. Multivariate analysis indicated the use of a pegIFN α-2a preparation ($P = 0.02$) and an HCV-RNA level of less than 800 KIU/mL as factors contributing to SVR. Also, the SVR rate was 65% in the group that showed a rapid virological response (RVR) and 0% in the non-RVR group ($P < 0.001$). It was shown that SVR cannot be attained in patients in whom early negative conversion of HCV-RNA cannot be achieved either by pegIFN α-2a or IFN α-2a.

Pharmacokinetics. The pharmacokinetics after a single subcutaneous administration of pegIFN α-2a at 90 μg in patients with a creatinine clearance of 20 mL/min or above was the same as in healthy adults. However, when pegIFN α-2a was administered once subcutaneously at 45, 90, 135, and 180 μg, its plasma concentration increased in a dose-related manner, and the pharmacokinetics in dialysis patients after the administration at 135 μg was similar to that in healthy adults after the administration at 180 μg (26).

In a report about patients in Japan, Cmax and Tmax after a single administration of pegIFN α-2a at 90 μg were similar to those in healthy adults after the administration at 180 μg, but the disappearance of the drug from blood was delayed. The increase in the plasma concentration was insufficient by a single administration of pegIFN α-2a at 45 μg. Also, the pharmacokinetics on repeated administrations of pegIFN α-2a at 90 μg were similar to those in healthy adults at 180 μg (27). Therefore, the dose of pegIFN α-2a in dialysis patients must be reduced to 90–135 μg.

3. Treatment with combination of pegIFN and ribavirin

There were four reports on treatment of dialysis patients with a combination of pegIFN and ribavirin by 2009 (28–31). pegIFN α-2a was administered initially at 135 μg once a week, and pegIFN α-2b was administered at 50 μg once a week, by subcutaneous injection. The SVR rate was 29–97%, the dropout rate was 0–71%, and the treatment was often discontinued due to severe anemia requiring transfusion. However, in reports with a high SVR rate, the dropout rate was low, and modifications such as an increase in the dose of an erythropoiesis stimulating agent (ESA) and the administration of ribavirin every other day were made.

Also, there is a report that ribavirin is excreted through the kidneys, that its AUC increases three times or more in patients with a creatinine clearance of less than 30 mL/min compared with patients with normal renal function, and that it cannot be eliminated efficiently by hemodialysis (32), so its administration to dialysis patients is a contraindication.

4. Guidelines for IFN therapy in dialysis patients

(1) Drugs and administration methods
- Subcutaneous injection of pegIFN α-2a at 90–135 μg once a week over 24–48 weeks
- Subcutaneous or intramuscular injection of natural IFN α or recombinant IFN α-2b at 3–6 million units once a day, 3 times a week, over 24–48 weeks
- Intravenous drip infusion (30–60 min) of natural IFN β at 3–6 million unites once a day, 3 times a week, over 24–48 weeks

(2) Comments about the guidelines

In dialysis patients undergoing IFN therapy, the SVR rate is similar to, or higher than, in patients with normal renal function, but the dropout rate from the treatment is also high. Factors important for achieving SVR are a low viral level, a genotype other than genotype 1, use of pegIFN, rapid virological response, and no marked liver fibrosis.

While the SVR rate is high in patients in whom the treatment could be continued, the dropout rate is higher in dialysis patients than in patients with normal renal function because of cytopenia and psychiatric symptoms. For achieving SVR, it is important to complete the treatment by promptly using an ESA preparation at a high dose in patients showing anemia and by concomitantly using granulocyte colony stimulating factor (G-CSF) and reducing the dose of IFN in patients showing neutropenia.

There has also been a report that a low dropout rate and a high SVR rate were obtained in dialysis patients by ribavirin combination therapy with reduced dose and number of administrations. This approach is likely to be effective in patients treated again after no response to IFN monotherapy and genotype 1 patients showing a high viral level. However, as ribavirin accumulates and cannot be eliminated by hemodialysis, the drug is contraindicated for dialysis patients by its package insert, and we recommend not administering it to dialysis patients.

Therefore, we recommend IFNα or IFNβ monotherapy as an antiviral therapy for dialysis patients. Regarding the drug selection for antiviral therapy using IFNα alone, the results of an RCT that the SVR rate was high, that adverse effects were infrequent, and that dropout rate was low with a pegIFNα preparation have been reported. We recommend using pegIFNα for treating dialysis patients. Although there are pegIFNα-2a and pegIFNα-2b, treatment using pegIFNα-2a monotherapy is covered by medical insurance in Japan.

5. *Other treatments*

Drugs of suppressing inflammation in the liver. In patients with normal renal function, Stronger Neo-Minophagen C (SNMC) or ursodeoxycholic acid (UDCA, Urso) are administered as drugs of suppressing inflammation to those with liver dysfunction in whom IFN therapy cannot be performed or has been ineffective. RCTs and prospective studies in patients with normal renal function have provided little evidence of suppression of death and liver cirrhosis or liver cancer (33,34), and there is no evidence in dialysis patients. In addition, as no antiviral effect is observed in drugs of suppressing inflammation, they are administered with the objective of reducing ALT in patients with liver dysfunction.

Administration methods

1 Stronger Neo-Minophagen injection, intravenous injection at 40–100 mL per injection, at each dialysis
2 Urso (100 mg), 6–9 tablets/day, daily oral administration t.i.d.

Virus removal and eradication by DFPP (VRAD). VRAD is covered by insurance in patients receiving re-treatment with IFN, those with genotype 1B, and those with an HCV-RNA level of 100 KIU/mL or higher up to five times (there is no evidence regarding the amount of treated plasma or duration, interval, or number of VRAD).

A multi-facility collaborative prospective study in non-dialysis patients is in progress, and SVR is compared between groups undergoing PEG-IFN plus ribavirin (30 patients) and PEG-IFN plus ribavirin plus DFPP (74 patients) (35). In the patients in whom SVR could be evaluated, SVR was observed in 50.0% (29/58) in the PEG-IFN plus ribavirin group and 70.8% (17/24) in the PEG-IFN plus ribavirin plus DFPP group. While the SVR rate was higher in the group treated by combinations including DFPP, the increase was not significant. There is no report comparing SVR between IFN therapy and a combination therapy including DFPP in dialysis patients, and there is no evidence. However, ribavirin administration to dialysis patients is a contraindication, and as VRAD is expected to be effective as a concomitant treatment in re-treatment using IFN, evaluation by accumulation of clinical research is necessary for the future.

[Comments concerning HCV-infected recipients of kidney transplantation]

1. *HCV infection and kidney transplantation*

Fabrizi et al. performed meta-analysis of 10 clinical studies and 2502 kidney transplantation patients and reported the incidences of diabetes after kidney transplantation in HCV-antibody-positive and -negative patients (36). The incidence of diabetes in HCV-antibody-positive patients varied from 7.9–50.0% among reports but was significantly higher than in negative patients with an odds ratio of 3.97 (95% confidence interval = 1.83–8.61, P-value = 0.047). The authors suggested the possibility that this is related to the kidney graft survival rate in HCV-antibody-positive patients.

Mathurin et al. reported the survival rate and graft survival rate 10 years after kidney transplantation in 834 patients (128 were HBs-antigen-positive, 216 were HCV-antibody-positive) (37). The survival rate 10 years after kidney transplantation was 65 ± 5% in HCV-antibody-positive patients and 80 ± 3% in HCV-antibody-negative patients ($P < 0.001$), and the graft survival rate was 49 ± 5% and 63 ± 3%

($P < 0.0001$), respectively, both being lower in the HCV-antibody-positive patients.

2. IFN therapy before transplantation

Kamar et al. performed standard IFN therapy in five HCV-antibody-positive and HCV-RNA-positive hemodialysis patients (38). SVR was observed in 21 (38%), and 16 (76%) of them underwent kidney transplantation. All patients continued to be HCV-RNA-negative throughout an observation period of 22.5 months (2–88 months), with none having developed post-transplantation diabetes.

Cruzado et al. evaluated the occurrence of post-transplantation nephritis in 78 HCV-antibody-positive dialysis patients after kidney transplantation (IFN therapy was performed before transplantation in 15 and not in 63) (39). In those who underwent IFN therapy, 10/15 (67%) showed SVR, and only one patient (6.7%), who could not attain SVR, developed post-transplantation nephritis. In those who did not undergo IFN therapy, 12/63 (19%) developed post-transplantation nephritis. The frequency of post-transplantation nephritis was reduced by IFN therapy before transplantation.

Mahmoud et al. reported the effects of IFN therapy before transplantation on rejection and renal function after transplantation in 50 HCV-RNA-positive kidney transplantation patients (40). The patients consisted of 18 who underwent IFN therapy and 32 who did not, and the percentage of those who showed chronic rejection was significantly higher, and the renal function 5 years after transplantation was significantly lower, in the non-IFN therapy group.

Interferon therapy before transplantation is important to improve the kidney graft survival rate.

3. IFN therapy after transplantation

Fabrizi et al. carried out a meta-analysis concerning 12 studies (102 patients) in which standard IFN therapy and standard IFN plus ribavirin therapy were performed after kidney transplantation (41). The SVR rate was 18.0% (95% CI: 7.0–29.0%), and the dropout rate was 35.0% (95% CI: 20–50%). The most frequent adverse effect was kidney graft dysfunction. IFN therapy after transplantation was unsatisfactory in both efficacy and safety.

4. Guidelines for IFN therapy in kidney transplanted patients

In HCV-infected recipients of kidney transplantation, the post-transplantation incidence of diabetes is high, and the graft survival rate and survival rate are low. IFN therapy before transplantation reduces the incidences of post-transplantation diabetes, post-transplantation nephritis, and chronic rejection. However, IFN therapy after kidney transplantation is associated with a low SVR rate and a high dropout rate, and induces rejection of the kidney graft.

Therefore, in HCV-infected dialysis patients expecting kidney transplantation, IFN therapy should be performed before transplantation. Also, in HCV-infected recipients of kidney transplantation, IFN therapy is likely to induce rejection and should be performed only when the necessity surpasses the risk (fibrosing cholestatic hepatitis [FCH] etc.).

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PREVENTION OF HCV INFECTION AT HEMODIALYSIS FACILITIES

[Statements]

1 It is recommended to apply and implement a strict infection control procedure to prevent blood-borne infection of pathogens including HCV at hemodialysis facilities. (Evidence level: Very low, Recommendation level: Strong)
2 In addition to a strict infection control procedure, it is recommended to identify or isolate HCV-infected patients and to use special dialysis instruments (consoles) for them. (Evidence level: Very low, Recommendation level: Strong)
3 It is recommended that the infection control procedure includes hygienic cautions to effectively prevent direct transmission of pathogens between patients through blood or body fluid or via contaminated gloves, medical materials, or instruments. (Evidence level: Very low, Recommendation level: Strong)
4 In evaluating the results of HCV infection prevention measures at hemodialysis facilities, it is recommended to include observation of the state of

implementation of infection control measures, periodic surveillance of the state of infection, and review of infection control measures depending on the state of infection. (Evidence level: Very low, Recommendation level: Strong)

[Comments]

1. It is recommended to apply and implement a strict infection control procedure to prevent blood-borne infection of pathogens including HCV at hemodialysis facilities. (Evidence level: Very low, Recommendation level: Strong)

The occurrence of nosocomial infection of HCV in dialysis facilities has been documented by epidemiological and viral molecular biological researches (1,2). The most frequent patient-to-patient transmission of HCV is caused by contamination of the drugs administered and the surface of instruments and materials in the dialysis facility including gloves due to manipulations violating the infection control procedure (1,2). With the current equipment, transmission of infection in the dialysis instruments is unlikely (3). Other causes of nosocomial infection include direct contact between patients and medical actions outside the dialysis facility such as transfusion (4), but their frequency is considered to be low. Therefore, for the prevention of HCV infection, it is required to determine and observe effective infection control procedures and to periodically review them and make necessary modifications (5–8). In Japan, the Manual Regarding the Standard Dialysis Procedure and Prevention of Nosocomial Infections in Dialysis Medicine (7) prepared with a Grant-in-Aid for Health and Welfare Science by the Ministry of Health, Labour and Welfare is used widely as a manual of infection control procedures at dialysis facilities.

2. In addition to a strict infection control procedure, it is recommended to identify or isolate HCV-infected patients and to use special dialysis instruments (consoles) for them. (Evidence level: Very low, Recommendation level: Strong)

Since infection experiments cannot be performed due to ethical restrictions, we must depend primarily on the results of observational studies. In Japan, the prevalence of HCV infection is clearly higher than in Western countries (9). On the basis of the results of a multi-facility observational study (9) that the incidence of new HCV infection is high at facilities with a high prevalence of HCV infection and that it is lower at facilities with a larger number of stations for isolated dialysis and the results of an observational study (10) that infection is less frequent at facilities that isolate HCV-infected patients than at those that do not isolate them, we recommend isolation of HCV-infected patients or the use of dedicated HD machines. While this statement differs from the CDC guidelines of the United States (5), these are considered to be necessary infection control measures from the high prevalence of HCV infection in Japan, poorer prognosis of HCV-positive dialysis patients (11), and statement of the German clinical nephrology working group in 2006 (8).

3. It is recommended that the infection control procedure includes hygienic cautions to effectively prevent direct transmission of pathogens between patients through blood or body fluid or via contaminated gloves, medical materials, or instruments. (Evidence level: Very low, Recommendation level: Strong)

According to the Ministry of Health, Labour and Welfare, each hospital must have an "Infection Control Manual" independently prepared by the Infection Control Committee. However, it is difficult for a small facility to prepare a manual, survey the state of infection, and continue its modification. Therefore, the "Manual Regarding the Standard Dialysis Procedure and Prevention of Nosocomial Infections in Dialysis Medicine" (7) was prepared with a Grant-in-Aid for Health and Welfare Science by the Ministry of Health, Labour and Welfare and with the cooperation of the Japanese Association of Dialysis Physicians, Japanese Society for Dialysis Therapy, Japan Association for Clinical Engineering Technologists, and Japan Academy of Nephrology Nursing as a manual of infection control procedure at dialysis facilities (8) and is used as a model of individual hospital manuals (12). In addition, there has been a report of the observation that the incidence of new HCV infection was reduced by its implementation (13).

There are reports that the risk of infection does not increase by the reuse of the dialyzer if it is handled by a professional agent or dedicated machines are operated by strict observance of reliable infection control procedures. In Japan, however, there is no professional agent or dedicated machine, and dialyzers, the cost of which is covered by insurance, are not permitted to be reused. Since infection is expected to increase unless dialyzers are reused with sufficient caution under these conditions (10), it is recommended not to reuse them.

4. In evaluating the results of HCV infection prevention measures at hemodialysis facilities, it is recommended to include observation of the state of implementation of infection control measures, periodic surveillance of the state of infection, and review of infection control measures depending on the state of infection. (Evidence level: Very low, Recommendation level: Strong)

According to the results of inspection of the dialysis operation at nine dialysis facilities in Spain in November 2003, the staff of the dialysis facilities wore gloves in 93% of the manipulations requiring gloves, but the hands were washed 36% of the times after, and only 14% of the times before, contact with patients (14). On direct observation of how infection control manipulations were implemented after an outbreak (15), problems including (i) poor compliance with hand-washing, (ii) poor compliance with glove changes particularly in emergency hemostasis of arteriovenous fistula, (iii) carrying a channel contaminated with blood in the dialysis room without containing it in a bag, (iv) neglect of periodic decontamination of blood-contaminated dialysis system, and (v) neglect of replacement of a contaminated pressure transducer protector were revealed, but these problems are hardly detected by interviews with the staff (16).

In evaluating the results of HCV infection prevention measures at hemodialysis facilities, it is recommended to observe the state of implementation of infection control measures, periodically survey the state of infection, and review infection control measures depending on the state of infection.

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CLINICAL REVIEW

Iron metabolic disorder in chronic hepatitis C: insights from recent evidence

Keisuke Hino · Sohji Nishina · Yuichi Hara

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Abstract The liver is the major iron storage organ in the body, and therefore iron metabolic disorder is sometimes involved in chronic liver diseases. Chronic hepatitis C is one of the liver diseases that show hepatic iron accumulation. The present review highlights the current concept of hepatic iron overload status in chronic hepatitis C and discusses how iron metabolic disorder develops in this disease, and the impact of hepatic iron overload on disease progression and its relevance to hepatocarcinogenesis. The level of hepatic iron accumulation in chronic hepatitis C should be recognized to be basically mild to moderate and sometimes within the normal range. However, even mild to moderate iron overload in the liver contributes to disease progression and hepatocarcinogenesis in chronic hepatitis C, probably by reinforcing the oxidative stress induced by hepatitis C virus (HCV) protein. The mechanisms by which hepatic iron overload develops in chronic hepatitis C have not been fully elucidated. Reduction of the transcription activity of hepcidin by HCV-induced reactive oxygen species may in part account for it, but the regulation of hepcidin is very complex and may depend on many variables, including the particular stage of the systemic and/or hepatic inflammatory conditions and the circulating transferrin-bound iron and intracellular iron stores. This might explain the variations in hepatic iron concentrations reported among patients with HCV-related chronic liver disease.

K. Hino (✉) · S. Nishina · Y. Hara
Department of Hepatology and Pancreatology,
Kawasaki Medical School, 577 Matsushimam, Kurashiki,
Okayama 701-0192, Japan
e-mail: khino@med.kawasaki-m.ac.jp

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Introduction

The liver is the major iron storage organ in the body, and therefore iron metabolic disorder is sometimes involved in chronic liver diseases. Chronic hepatitis C is one of the liver diseases that show hepatic iron accumulation [1], even though the level of hepatic iron is not extremely high as observed in hereditary hemochromatosis [2]. Patients with chronic hepatitis C virus (HCV) infection frequently have elevated serum ferritin and hepatic iron levels [3]. Excess divalent iron can be highly toxic, mainly via the Fenton reaction producing hydroxyl radicals [4]. This is particularly relevant for chronic hepatitis C, in which oxidative stress has been proposed as a major mechanism of liver injury. Oxidative stress and increased iron levels strongly favor DNA damage, genetic instability, and tumorigenesis. Indeed, Kato et al. [5, 6] reported that phlebotomy lowered the risk of progression to hepatocellular carcinoma (HCC), which showed the critical role of iron in the development of HCC in patients with chronic hepatitis C. Thus, there is a critical interaction between HCV infection and hepatic iron overload in the progression of liver disease and the development of HCV-related HCC. However, the mechanisms underlying hepatic iron overload and its contribution to hepatocarcinogenesis in chronic hepatitis C are not fully elucidated. The present review highlights the current concept of hepatic iron overload status in chronic hepatitis C, and discusses how iron metabolic disorder develops in chronic hepatitis C and the impact of hepatic iron overload on disease progression and its relevance to hepatocarcinogenesis.

Hepatic iron accumulation

Most of the body's excess iron is stored in the liver, and in the normal adult male, liver iron stores can range from 0.5 to 1 g [7]. The hepatic iron concentration in normal liver tissue obtained at autopsy has been reported to be 16.51 (7.82–39.93) mmol/kg dry tissue [median and (5–95 percentile interval)] [8]. These values are estimated to be equivalent to a hepatic iron content of 300–900 μg/g dry weight liver tissue. Extensive studies reported median hepatic iron concentrations of 396 (range 0–2,105) and 458 (range 114–2,190) μg/g dry weight liver tissue in patients with chronic hepatitis C [9, 10]. In addition, the reported percentages of patients with hepatic iron concentrations ≥1,000 μg/g dry weight were 14 and 19 %, respectively [9, 10]. Therefore, it should be noted that among patients with chronic hepatitis C some have high hepatic iron content, whereas others have normal hepatic iron content. In contrast, a hepatic index (μmol Fe/g liver tissue/patients age) of 1.9 or more has been reported to be typical of patients with hereditary hemochromatosis [11]. If the hepatic index of a patient aged 60 with hereditary hemochromatosis is 1.9, the hepatic iron concentration of this patient is assumed to be 6,384 μg/g liver tissue. Thus, we should understand that hepatic iron content is much less in chronic hepatitis C than in hereditary hemochromatosis and within the normal range in some of patients with chronic hepatitis C, even though it is recognized to be one of liver diseases that show hepatic iron accumulation.

There also remains uncertainty as to whether iron predominantly accumulates in hepatocytes or the reticuloendothelial system, mainly Kupffer cells, in patients with chronic hepatitis C. Some clinical studies showed that iron was mainly localized in the reticuloendothelial system [1, 12], whereas others reported its localization in hepatocytes [13]. Interestingly, Fiel et al. [14] documented that even ribavirin-associated hemolysis deposited iron preferentially in hepatocytes in patients with chronic hepatitis C. Hepatocytic iron accumulation may indicate potential DNA damage and genetic instability in association with HCV-induced oxidative stress, while iron deposition in Kupffer cells may contribute to cytokine release, leading to inflammation or fibrosis. However, further investigations are needed to clarify this issue.

Hepcidin expression

Hepcidin, which was originally isolated from human serum and urine as a peptide with antimicrobial activity [15, 16], is a hormone exclusively synthesized in the liver and a negative regulator of iron release into the systemic circulation by duodenal enterocytes and reticuloendothelial macrophages [17, 18]. Hepcidin binds to the iron exporter ferroportin, which results in internalization and degradation of ferroportin [19]. The lack of hepcidin expression in knockout mice leads to iron overload [20], and conversely, overexpression of hepcidin in transgenic mice causes severe iron deficiency [21]. Iron transferrin also regulates hepcidin synthesis through hemojuvelin and bone morphogenetic protein (BMP) 2/4 [22].

Fujita et al. [23] showed for the first time that hepatic hepcidin mRNA levels adjusted by serum ferritin values were significantly lower in patients with chronic hepatitis C than in those with chronic hepatitis B or those without hepatitis B virus (HBV) or HCV infection. Of note, the relative expression of hepcidin for iron stores was lower in chronic hepatitis C than in chronic hepatitis B or chronic liver diseases without HBV or HCV infection, even though hepcidin expression levels were strongly correlated with serum ferritin and the degree of hepatic iron deposition. These results suggested that hepcidin might play a pivotal role in iron overload in patients with chronic hepatitis C. A recent study using a validated immunoassay of the 25-amino acid bioactive hepcidin in serum also revealed that serum hepcidin levels were lower in patients with chronic hepatitis C than in controls despite a significant correlation between hepcidin and serum ferritin or the histological iron score in both groups [24]. Thus, the relatively decreased synthesis of hepcidin in chronic hepatitis C contrasts with the absolute deficit or lack in hepcidin synthesis observed in hereditary hemochromatosis and may account for the mild to moderate hepatic iron overload observed in some patients with chronic hepatitis C.

Mechanisms underlying hepatic iron accumulation

Elucidating the mechanisms of iron accumulation in chronic hepatitis C may provide new tools for the management of the condition or for the prevention of its complications, or both. Hepcidin appears to provide a critical clue for elucidating the mechanisms of iron accumulation because its decreased synthesis has been reported in chronic hepatitis C in previous studies [23–25]. Disruption of hepcidin regulation resulting from inhibited activity of the transcription factor CCAAT/enhancer-binding protein α (C/EBPα) has been postulated as a possible mechanism causing iron overload in alcoholic liver disease [26, 27]. We investigated the mechanism by which hepatic iron accumulates using transgenic mice expressing the HCV polyprotein [28]. These mice had reduced hepcidin mRNA expression, which was attributed to HCV protein-induced reactive oxygen species (ROS), with consequent upregulation of an inhibitor of the binding of C/EBPα to the hepcidin promoter. Thus, the mechanisms underlying HCV-related hepatic iron overload appear to have some similarities with alcohol-induced iron overload

in terms of disrupted hepcidin transcription through suppressed activity of C/EBPα. In agreement with our observation, an in vitro study by Miura et al. [29] using hepatoma cells showed that HCV-induced ROS inhibited the binding activity of C/EBPα to the hepcidin promoter through increased histone deacetylase activity.

Hepcidin is transcriptionally regulated in response to the iron concentration, inflammation, hypoxia, and erythropoiesis [30]. BMPs, members of the transforming growth factor beta superfamily, play a crucial role in regulating hepcidin transcription through SMAD signaling [31–33]. Hepcidin is regulated by both the circulating transferrin-bound iron and intracellular iron stores. Its exact pathway is still unknown but seems to involve the BMP pathway. As yet there is no convincing evidence that accounts for the suppressive transcription of hepcidin through the BMP/SMAD cascade in chronic hepatitis C. The significant correlations between hepcidin and serum ferritin or the histological iron score in chronic hepatitis C [23, 24] suggest that hepcidin transcription is properly regulated in response to the iron concentration in chronic hepatitis C. Thus, hepcidin transcription in chronic hepatitis C may be potentially regulated by the opposing effects of HCV-induced hepcidin-suppressive factors and the iron load-induced hepcidin-stimulation factors. As suggested by Girelli et al. [24], in the early phase of chronic hepatitis C, hepcidin may be prominently suppressed by HCV but, as iron accumulates, the negative influence of viral factors may be masked by the positive stimulation of iron.

Inflammation also regulates hepcidin transcription. Proinflammatory cytokines such as IL-6 mediate this response by inducing transcription of hepcidin mRNA via STAT3, which binds to a STAT-responsive element within the hepcidin promoter [34–36]. Our transgenic mice expressing the HCV polyprotein did not show any inflammation in the liver. A possible pitfall in this experimental model was that we could not take the inflammatory effect on hepcidin regulation into account, which is different from what is observed in patients with chronic hepatitis C. Serum levels of IL-6 have been shown to be elevated in patients with HCV-related chronic liver disease [37], which raises the possibility that IL-6 acts to stimulate hepcidin expression through the STAT3 pathway. This would be expected to counteract the decrease in hepcidin transcription caused by HCV-induced ROS. However, no significant relationship has been found between serum IL-6 and hepcidin in patients with chronic hepatitis C [24, 38], even though a paracrine effect of local IL-6 release on hepcidin transcription in the liver cannot be excluded. On the other hand, chronic inflammation with production of proinflammatory cytokines has the potential to deliver an additional burden of ROS, which would be expected to reinforce the decrease in hepcidin transcription. Most likely, during chronic inflammation states in vivo like chronic hepatitis C, the regulation of hepcidin is more complex and may depend on many variables, including the particular stage of systemic and/or hepatic inflammatory disease. This might explain the variations in hepatic iron concentrations reported among patients with HCV-related chronic liver disease. As an iron regulatory molecule other than hepcidin, upregulation of transferrin receptor 1 has been reported in patients with chronic hepatitis C [39]. The schematic outline in Fig. 1 depicts the assumed mechanisms underlying the hepatic iron accumulation in chronic hepatitis C.

Impact of hepatic iron overload on disease progression and relevance to hepatocarcinogenesis

Iron is a cofactor that influences the severity and progression of nonhemochromatic liver diseases, especially steatohepatitis and viral hepatitis [40–44]. The importance of iron as a comorbidity factor in chronic hepatitis C is emphasized by several reports of more fibrosis and a greater risk of HCC development with more hepatic iron [45–47]. Recently, it has been prospectively shown in the HALT-C (hepatitis c anti-viral long-term treatment to prevent cirrhosis) trial cohort that stainable iron in hepatocytes and portal tract cells predicts progression and outcomes (Child Pugh score >7, ascites, encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, HCC, death) in advanced chronic hepatitis C [48].

Although the association of markedly increased iron accumulation in the liver with hepatocarcinogenesis in hereditary hemochromatosis has been well described [49], it remains to be elucidated whether mild to moderate increases in hepatic iron accumulation contribute to the development of HCC in patients with HCV-associated chronic liver diseases. To determine the mechanisms underlying the development of HCC in the presence of both HCV infection and mild to moderate hepatic iron accumulation, we investigated whether iron overload equivalent to that in chronic hepatitis C patients contributed to the development of HCC in transgenic mice expressing the HCV polyprotein [50]. Transgenic mice fed an excess-iron diet showed marked hepatic steatosis, including the centrilobular microvesicular type, ultrastructural alterations of the mitochondria, and decreased degradation activity of fatty acid at 6 months, as well as hepatic accumulation of lipid peroxidation products and 8-hydroxy-2′-deoxyguanosine (8-OHdG) at 12 months after the initiation of feeding. Of note, hepatic tumors including HCC developed in 5 of 11 (45 %) transgenic mice fed the excess-iron diet but not in control mice or transgenic mice fed the control diet at 12 months after the initiation of feeding. These results indicated the importance

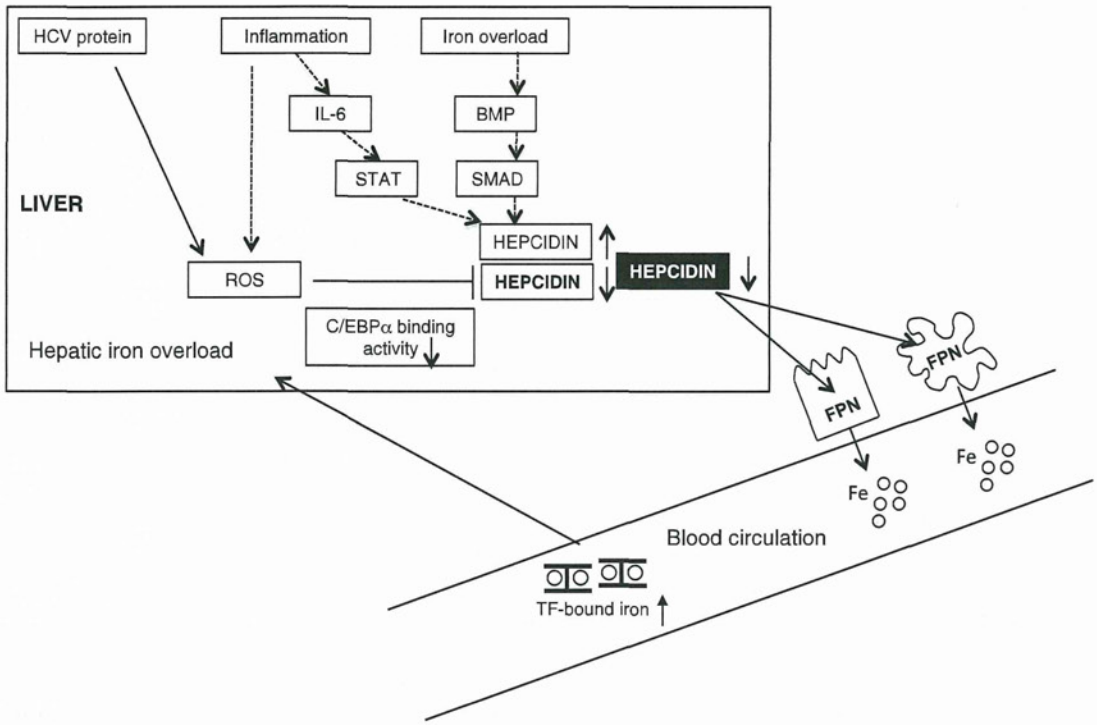

Fig. 1 Schematic diagram depicting the mechanisms underlying hepatic iron accumulation. HCV protein-induced ROS reduces hepcidin transcription through inhibition of DNA binding activity of C/EBPα. Hepcidin transcription in chronic hepatitis C may be potentially regulated by the opposing effects of HCV-induced hepcidin suppressive factors and iron load-induced hepcidin stimulation factors. Inflammation may also have the opposing effects of stimulation and suppression of hepcidin transcription through the IL-6/STAT pathway and ROS pathway, respectively. Decreased hepcidin expression enhances ferroportin (*FPN*) expression in the duodenum and macrophages, resulting in increased duodenal iron transport and macrophage iron release, which lead to hepatic iron accumulation

of oxidative stress and subsequent mitochondrial injury synergistically induced by iron loading and HCV proteins in the development of HCC. Tanaka et al. [44] showed a strong correlation of hepatic 8-OHdG levels with body and hepatic iron storage in patients with chronic hepatitis C and that oxidative DNA damage in the liver was associated with an increased risk of HCC development. Kato et al. [5] also reported that the decrease in hepatic 8-OHdG content caused by phlebotomy lowered the risk of progression to HCC, which indeed showed the critical role of the iron-overload state in the development of HCC in patients with chronic hepatitis C. Thus, there is a close relationship between oxidative DNA damage synergistically induced by hepatic iron accumulation and HCV proteins in the development of HCC in patients with HCV associated with chronic liver diseases. Whether long-term and sustained iron reduction by phlebotomy could help to prevent or delay disease progression and/or development of HCC is an important and still unresolved question, but a promising effect of phlebotomy was reported in a long-term nonrandomized prospective study [6]. As iron reduction and adherence to a low-iron diet are relatively easy and safe, combination of these treatments would seem to be beneficial to patients who cannot tolerate or have not responded to peginterfeon plus ribavirin therapy to prevent disease progression and/or the development of HCC.

Conflict of interest The authors disclose no conflicts of interest.

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Letter to the Editor

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Incidence of hepatocellular carcinoma and response to interferon therapy in HCV-infected patients: effect of factors associated with the therapeutic response and incidence of HCC

To the Editor:

Several previous studies reported a significantly lower incidence of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients who showed sustained virological response (SVR) to or relapsed on antiviral therapy with interferon (IFN) or peginterferon (PEG-IFN), with or without ribavirin compared with no responders (NR; i.e. partial response, viral breakthrough, or null-response) (1, 2). The reduction in HCC incidence was especially marked in patients with SVR. These results have been taken as evidence that antiviral therapy has an effect of suppressing the development of HCC.

Recently reported viral and host factors that are strongly associated with response to anti-HCV therapy (3, 4) may also be associated with the pathogenesis of HCC. Amino acid substitution in the HCV core region, a viral factor reportedly associated with response to PEG-IFN and ribavirin therapy (3), is also associated with the development of HCC (5). Regarding host factors associated with response to anti-HCV therapy (4), genetic polymorphisms near the *IL28B* gene are reportedly associated with hepatic steatosis (6) and interact with amino acid substitutions in the HCV core region (7), both of which are associated with the development of HCC (5, 8).

We analysed the incidence of HCC in 448 patients who completed anti-HCV therapy with IFN or PEG-IFN and in whom the genetic polymorphisms near *IL28B* gene were analysed after the approval of the hospital ethics committee and obtaining written informed consent. We found significant differences in the incidence of HCC between patients with SVR ($n = 247$), relapse ($n = 122$), and NR ($n = 79$) (Fig. 1A, $P < 0.0001$ by Log-rank test). However, the prevalence of patients having TT genotype at rs8099917 near the *IL28B* gene, which is associated with favourable response to anti-HCV therapy, was significantly lower in patients with NR (SVR, 85.8%; relapse, 80.3%; NR, 39.2%; $P < 0.0001$ by Chi-square test). In addition, we found significant differences in the incidence of HCC also according to the genotype of rs8099917 (Fig. 1B, $P = 0.0156$). Although multivariate analysis using Cox proportional hazard model including age, gender, HCV genotype, and the outcome of therapy, but not *IL28B* polymorphisms identified SVR ($P = 0.0083$) and relapse ($P = 0.0493$) as independent factors that were associated with lower incidence of HCC, it failed to detect an independent factor that was associated with the incidence of HCC when *IL28B* polymorphisms were included. These results suggested that the previously reported differences in the incidence of HCC by anti-HCV response may not have been due to the ability of antiviral therapy to suppress HCC, but rather simply they may reflect the ability of such treatment to better identify patients at high-risk for HCC based on response to anti-HCV therapy.

It is not elucidated whether the results in our present analyses were simply due to the small number of

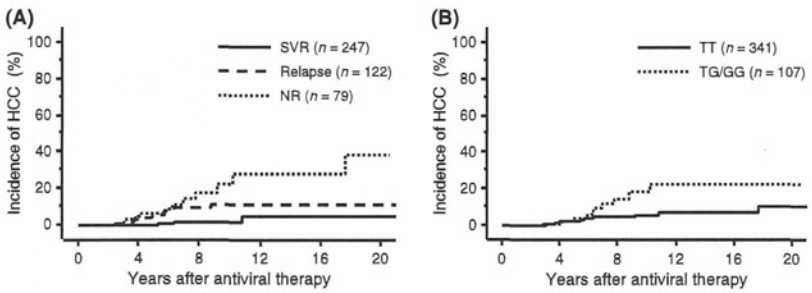

Fig. 1. Cumulative incidence of hepatocellular carcinoma (HCC) after antiviral therapy with interferon or peginterferon. (A) Incidence of HCC is significantly lower in patients with sustained virological response (SVR), those with relapse, and those with no response (NR) that includes partial response, viral breakthrough, or null-response, in that order. (B) Incidence of HCC is significantly lower in patients with TT genotype at rs8099917 near the *IL28B* gene, which is associated with the favourable response to antiviral therapy.

patients analysed or the incidence of HCC after antiviral therapy is similar regardless of response, when they are stratified by host and viral factors. In addition, our present analyses failed to examine the association between amino acid substitutions in the HCV core region and the incidence of HCC due to the small number of patients in whom the information of this substitution was available. Nonetheless, with the emergence of factors that can be independently associated with both the response to antiviral therapy and the development of HCC, the effect of response to antiviral therapy with IFN or PEG-IFN on the incidence of HCC will require re-examination taking *IL28B* polymorphisms and amino acid substitutions in the HCV core region into consideration.

Hidenori Toyoda and Takashi Kumada
Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

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大垣市民病院におけるEOB-MRIの肝細胞相で検出される乏血性結節の自然経過*

多田 俊史[1)] 熊田 卓 桐山 勢生 谷川 誠 豊田 秀徳
久永 康宏 金森 明 曽根 康博[2)] 小川 定信[3)]

Key Word Gd-EOB-DTPA, MRI, 肝細胞癌, 肝細胞相, 多血化

要旨

EOB-MRIの肝細胞相で検出される乏血性結節の自然経過，特に多血化に関する検討を行った．対象はEOB-MRIにて認められた乏血性の49結節である．経過観察中に多血化が認められた多血群は13結節(26.5%)，多血が認められなかった非多血群は36結節(73.5%)であり，1年間における対象全体の多血化率は43.4%であった．続いて1年間の多血化率を結節径が15 mmを超えるものと，それ以下のものに分類して評価すると前者が77.3%，後者が16.9%と有意に前者の多血化率が高いという結果であった($p=0.0174$)．さらにCox比例ハザードモデルで多変量解析をしたところ，結節径15 mm以下/超の項目がハザード比：2.03137，95%信頼区間：1.09571～3.76603，$p=0.0244$で多血化に関与する因子として選択された．

肝胆膵画像 2012；14：345-350

はじめに

Gd-EOB-DTPA造影MRI(EOB-MRI)により肝細胞癌の画像診断は大きな転換期を迎えた．特にGd-EOB-DTPA造影剤(EOB・プリモビスト®)の最大の特徴は投与後10～15分後(肝機能低下例はさらに長時間の場合もあり)に撮像される肝細胞相である．この肝細胞相での肝細胞癌の検出能は非常に高く，筆者らの検討[1]ではCTAP(CT during arterial portography)/CTHA(CT during hepatic arteriography)をゴールドスタンダードとして診断された小さな典型的肝細胞癌においても，肝細胞相での検出率は10 mm以下で100%，11 mm～20 mmで98.3%，21 mm～30 mmで96.3%と非常に良好な検出能であった．近年，肝細胞相で低信号を呈し，dynamic studyにおいて染影が認められない，いわゆる乏血性肝結節の取り扱いが注目されている．

以前，筆者らの検討[2]において，肝細胞相で低信号を呈し，CTHAで乏血性と診断された肝腫瘍8結節の腫瘍生検では全例が高分化型肝細胞癌であった．本邦からはSanoら[3]によっても同様の報告がなされたり，CTHAで認められた多血性fociのEOB-MRIの診断能の報告[4]もみられる．このような乏血性結節の治療タイミングについては臨床上，しばしば問題になる．最近ではこのような乏血性結節に対しては，ほかのモダリティで多血性の有無を確認し

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* Evolution of hypointense hepatocellular nodules observed only in the hepatobiliary phase of gadoxetate disodium-enhanced MRI

1) 大垣市民病院 消化器内科 (〒503-8502 岐阜県大垣市南頬町4-86)
Toshifumi TADA, Takashi KUMADA, Seiki KIRIYAMA, Makoto TANIKAWA, Hidenori TOYODA, Yasuhiro HISANAGA, Akira KANAMORI : Department of Gastroenterology Ogaki Municipal Hospital, *Gifu*
2) 大垣市民病院 放射線科
Yasuhiro SONE : Department of Radiology, Ogaki Municipal Hospital, *Gifu*
3) 大垣市民病院 医療技術部診療検査科
Sadanobu OGAWA : Department of Clinical Research, Ogaki Municipal Hospital, *Gifu*

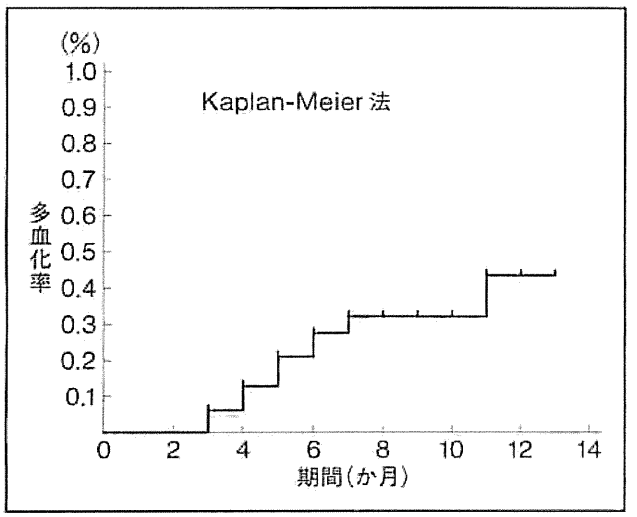

図1　対象結節全体の多血化率

たり，造影超音波の後血管相における Kupffer 細胞へのソナゾイド®の取り込み所見などを参考にして治療方針を決定することがすすめられている[3]．今回，当院で経験した乏血性肝結節の自然経過について，特に多血化に関する検討を行った．

対象と方法

対象は 2008 年 2 月～2009 年 7 月までに当院にて EOB-MRI が施行された 797 例中，繰り返し MRI が行われた 30 症例である．男性 19 例，女性 11 例で年齢中央値は 73 歳(58～81)であった．成因は C 型 25 例，非 B 非 C 4 例，B 型+C 型 1 例であった．また AFP(α-fetoprotein)の中央値は 7.35 ng/ml (0.8～287.7)で，PIVKA-II (protein induced by vitamin K antagonist-II)の中央値は 29.0 mAU/ml(10.0～791.0)であった．観察期間中央値は 5 か月(3～13)で，MRI の施行回数中央値は 3 回(2～9)であった．今回の対象の中には EOB・プリモビスト®発売当初の撮像条件が検討中である症例も含まれるため，明らかに低信号と認識できる 8 mm 以上を対象とした．そのうち，dynamic study で濃染所見が認められず，かつ肝細胞相で低信号を呈した，いわゆる乏血性結節は 49 結節であった．なお，再現性に乏しい低信号結節は検討から除外した．

MRI 装置は PHLIPS 社製 Achieva 1.5T Nova Dual を使用した．EOB・プリモビスト®は 0.1 ml/kg を 1.5 ml/秒で注入し，後押し用の生理食塩水は 35 ml を 2 ml/秒で注入した．造影前 T1 強調像は FFE(fast field echo)の dual echo 法にて in phase および opposed phase を，dynamic study は TFE (turbo field echo)の 3 D 収集にて動脈 2 相，門脈相，後期相の計 4 相を撮像し，造影後は TSE(turbo spin echo)法にて T2 強調像，TFE の 3 D 収集にて肝細胞造影相の順に撮像し，dynamic study の撮影を開始するタイミングは bolus traking 法を用い，腹部大動脈の濃染を確認後とし，肝細胞相は 15 分後に撮像した．

結果

対象結節の結節径の中央値は 15 mm(8～40)であった．また肝の他部位に典型的な肝細胞癌が存在したのは 16 結節であった．T1 強調画像では高信号 13 結節，等信号 31 結節，低信号 5 結節で，T2 強調画像では高信号 4 結節，等信号 40 結節，低信号 5 結節であった．

経過観察中に多血化が認められた多血群は 13 結節(26.5%)，多血が認められなかった非多血群は 36 結節(73.5%)で，それぞれの観察期間は 5 か月(3～11)，6 か月(3～13)であった．多血化の確認は EOB-MRI が 21 結節，造影超音波が 15 結節，血管造影下 CT が 13 結節であった．

また各群における結節径は，多血群が 20 mm (12～40)，非多血群が 14 mm(8～40)で，$p=0.0260$ と有意に多血群の結節径が大きいという結果であった．1 年間における対象全体の多血化率は 43.4%であった(図 1)．

多血化の濃染パターンは，結節全体が周囲肝実質に比し明らかに強く濃染(高信号)された場合を whole，結節全体が肝実質よりやや強く濃染(高信号)された場合を weak，結節の辺縁部のみ濃染(高信号)された場合を peripheral，結節の一部に濃染(高信号)を認めた場合を spot と分類した(図 2)．Dynamic study における多血群の濃染パターンを図 2 に従い分類した結果，結節全体が濃染する whole もしくは weak が 62%を示し，次いで peripheral，spot の順であった(図 3)．なお評価に用

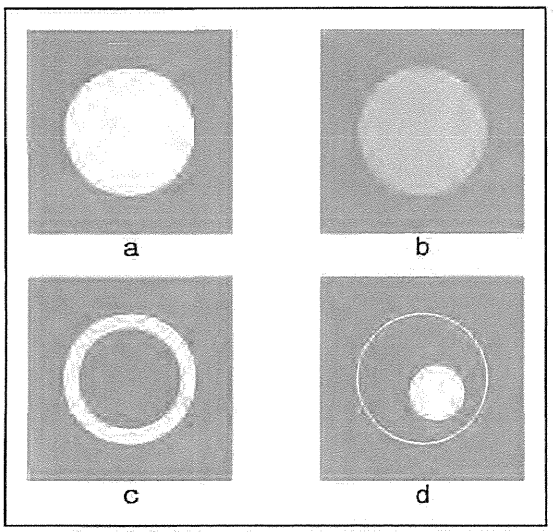

図2　多血時の濃染パターン
a. whole, b. weak, c. peripheral, d. spot.

いたのは動脈2相のうち最も濃染が強い時相とした.

続いて以前の当院の検討[5]をもとに1年間での多血化率を結節径が15 mmを超えるものと,それ以下のものに分類して評価すると前者が20結節で77.3%,後者が29結節で16.9%と有意に前者の多血化率が高いという結果であった($p=0.0174$, Log-rank test)(図4).

さらに結節径15 mm以下(29結節)/超(20結節),肝細胞癌併存あり(16結節)/なし(33結節),T1強調画像で低信号(5結節)/非低信号(44結節),T2強調画像で高信号(4結節)/非高信号(45結節)を投入因子としてCox比例ハザードモデルで多変量解析をしたところ,結節径15 mm以下/超の項目がハザード比:2.03137,95%信頼区間:1.09571～3.76603, $p=0.0244$で多血化に関与する因子として選択された(表1).

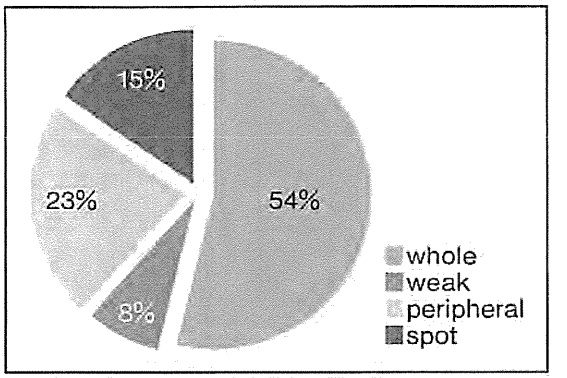

図3　濃染パターンの結果(図2より)

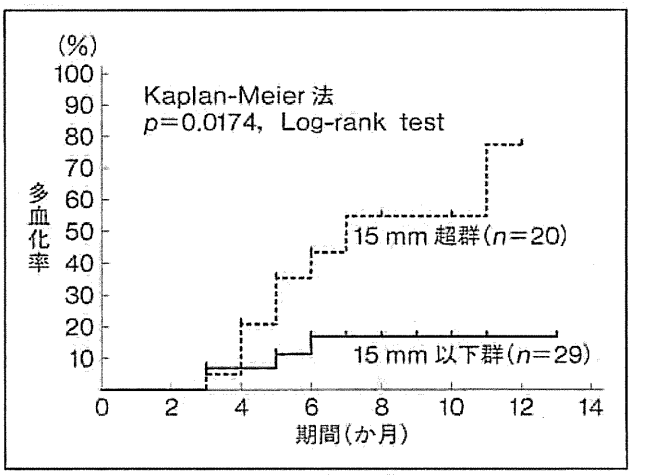

図4　結節径15 mm以下/超別の多血化率

症例

(症例1)　S8初回検出時の結節径は14 mmで,多血化までの観察期間は5か月

初回のdynamic studyでは明らかな初期濃染は認めなかったが,肝細胞相では境界明瞭な低信号として描出された.5か月後,同結節はdynamic study

表1　多血化に関する多変量解析(Cox比例ハザードモデル)

	ハザード比	95%信頼区間	p値
腫瘍径15 mm以下($n=29$)/超($n=20$)	2.03137	1.09571～3.76603	0.0244
肝細胞癌併存あり($n=16$)/なし($n=33$)	1.57614	0.39471～6.29381	0.5195
T1強調画像で低信号($n=5$)/非低信号($n=44$)	1.49623	0.22342～10.0201	0.6779
T2強調画像で高信号($n=4$)/非高信号($n=45$)	3.10060	0.58017～16.5703	0.1857

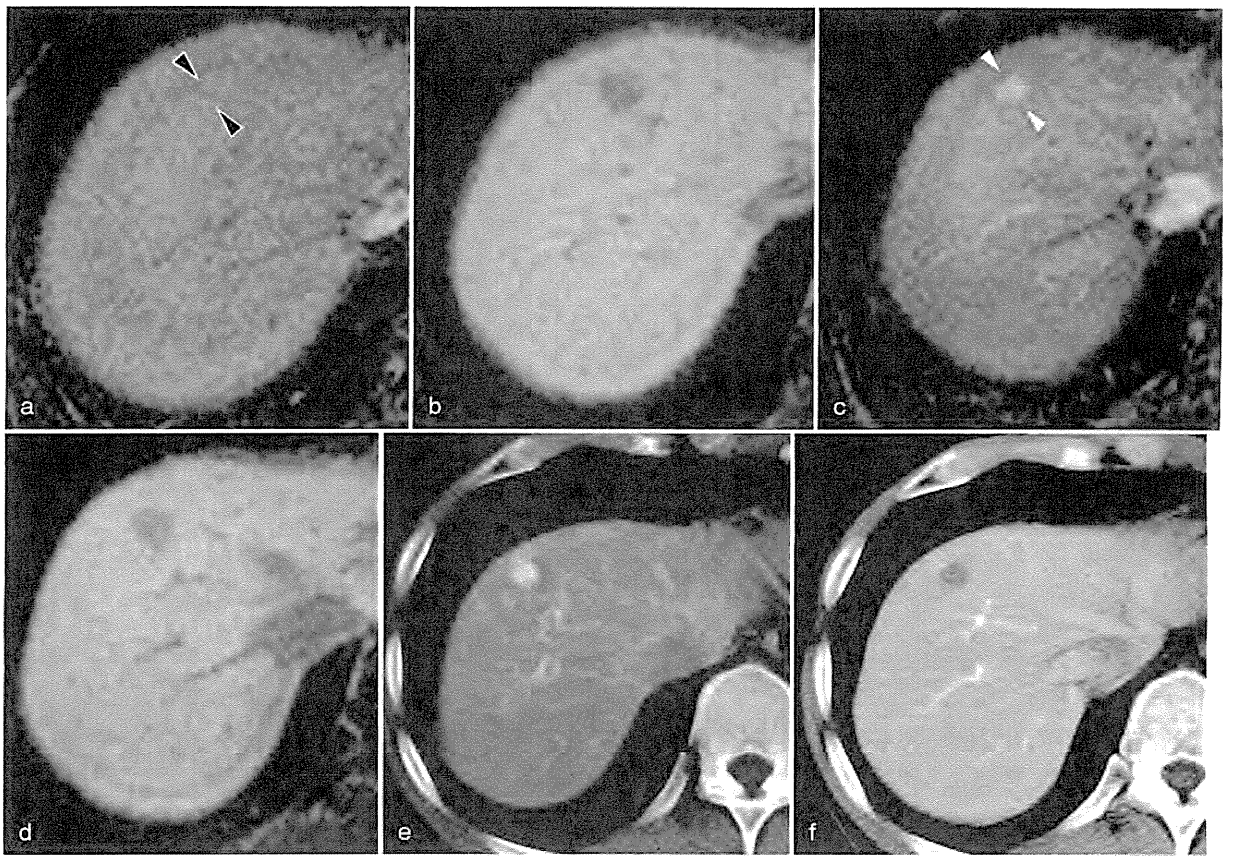

図5 〔症例1〕
a．初回動脈相，b．初回肝細胞相，c．多血時動脈相，d．多血時肝細胞相，e．多血時CTHA，f．多血時CTAP．
初回のdynamic studyでは濃染所見を認めなかったが(a，▶)，肝細胞相では境界明瞭な低信号として描出された(b)．5か月後，同結節はdynamic studyにて高信号が確認された(c，▷)．肝細胞相での結節径に著変は認められなかった(d)．同時期に施行された血管造影下-CTでも，CTHAでは高吸収を認め(e)，CTAPで低吸収を示した(f)．

にて高信号を示した．なお肝細胞相での結節径に著変は認めなかった．ほぼ同時期に施行された血管造影下-CTでも，同結節はCTHAでは高吸収を認め，CTAPで低吸収を示した(図5)．

〔症例2〕 S6初回検出時の結節径は8 mmで，多血化までの観察期間は6か月

初回のdynamic studyでは明らかな初期濃染は認めなかったが，肝細胞相では境界明瞭な低信号として描出された．6か月後，同結節はdynamic studyにて高信号を示した．肝細胞相では，初回に比べサイズの増大が確認され，内部点状の高信号を認めた．3か月後に施行された血管造影下-CTでも，同結節はCTHAでは高吸収を認め，CTAPで低吸収を示した(図6)．

〔症例3〕 S8初回検出時の結節径は9 mmで，多血化までの観察期間は4か月

初回のdynamic studyでは明らかな初期濃染は認めなかったが，肝細胞相ではやや境界明瞭な低信号として描出された．4か月後，同結節はdynamic studyにて結節辺縁に高信号を示した．肝細胞相では，初回に比べ辺縁の明瞭化，サイズの増大が確認された(図7)．

〔症例4〕 S8初回検出時の結節径は15 mmで，多血化までの観察期間は5か月

初回のdynamic studyでは明らかな初期濃染は認めなかったが，肝細胞相では境界明瞭な低信号として描出された．5か月後，同結節はdynamic studyにて結節内に複数の高信号を示した．なお肝細胞相での結節径は軽度増大を認めた(図8)．

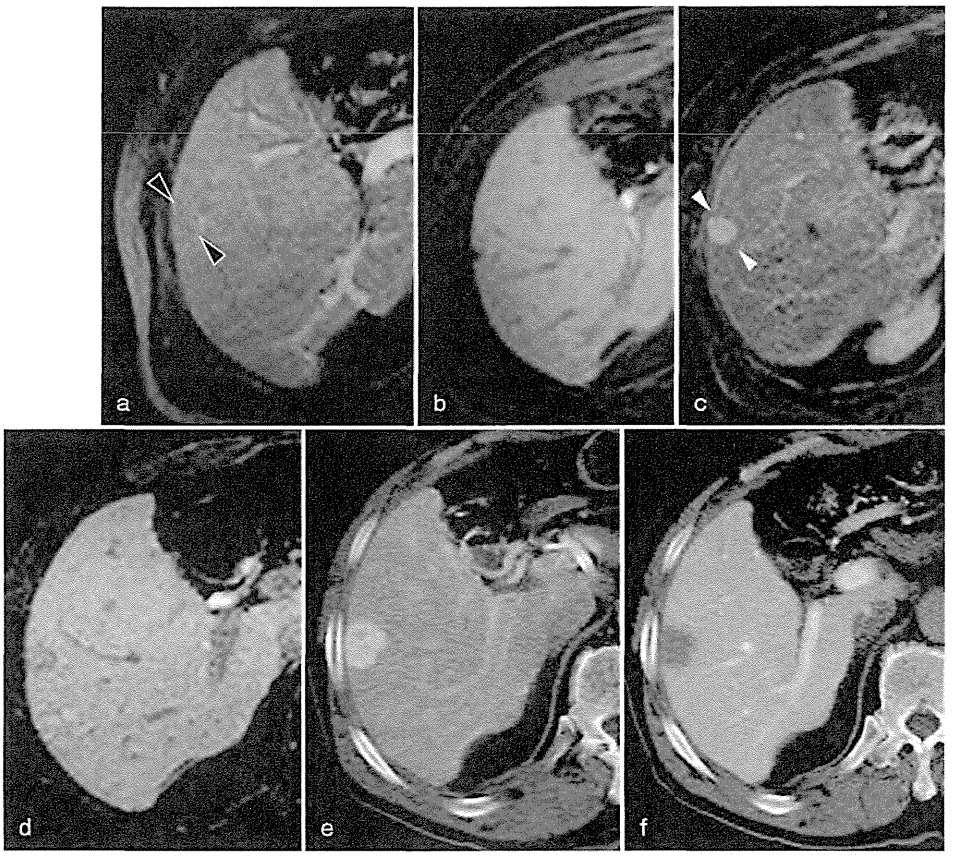

図6 〔症例2〕
a. 初回動脈相，b. 初回肝細胞相，c. 多血時動脈相，d. 多血時肝細胞相，e. 多血時CTHA，f. 多血時CTAP.
初回のdynamic studyでは濃染を認めなかったが(a, ▶)，肝細胞相では小さな低信号として描出された(b)．5か月後，同結節はdynamic studyにて高信号が確認された(c, ▷)．肝細胞相での低信号は増大を示した(d)．3か月後に施行された血管造影下-CTでも，CTHAでは高吸収を認め(e)，CTAPで低吸収を示した(f)．この時点で結節は著明な増大が確認された．

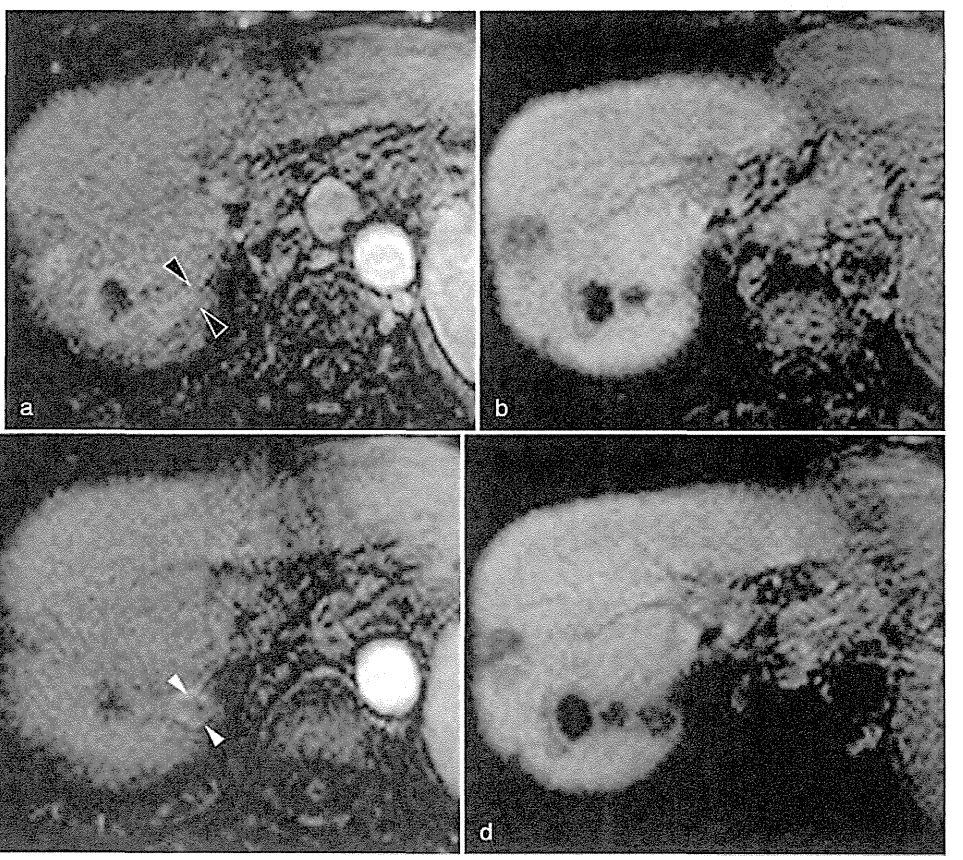

図7 〔症例3〕
a. 初回動脈相，b. 初回肝細胞相，c. 多血時動脈相，d. 多血時肝細胞相．
初回のdynamic studyでは濃染を認めなかったが(a, ▶)，肝細胞相ではやや境界明瞭な低信号として描出された(b)．4か月後，同結節はdynamic studyにて結節辺縁に高信号を示した(c, ▷)．肝細胞相では，初回に比べ辺縁の明瞭化，サイズの増大が確認された(d)．

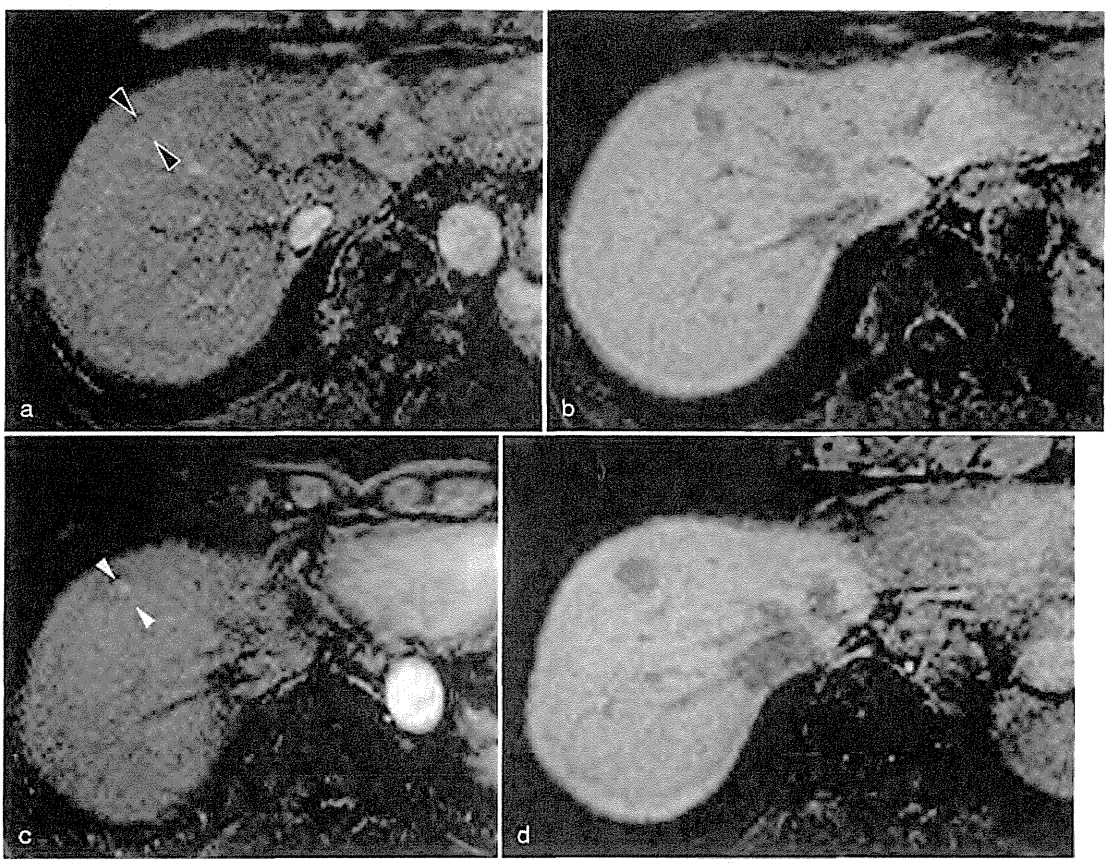

図8 〔症例4〕
a. 初回動脈相, b. 初回肝細胞相, c. 多血時動脈相, d. 多血時肝細胞相.
初回の dynamic study では濃染を認めなかったが(a, ▶), 肝細胞相では小さな低信号として描出された(b). 5か月後, 同結節は dynamic study にて高信号が確認された(c, ▷). 肝細胞相での低信号は増大を示した(d).

おわりに

結節径が15 mmを超えるEOB-MRIの肝細胞相で検出される乏血性結節は, 多血化のリスクが高く, 頻回の検査施行をはじめとして, 十分な注意が必要である.

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