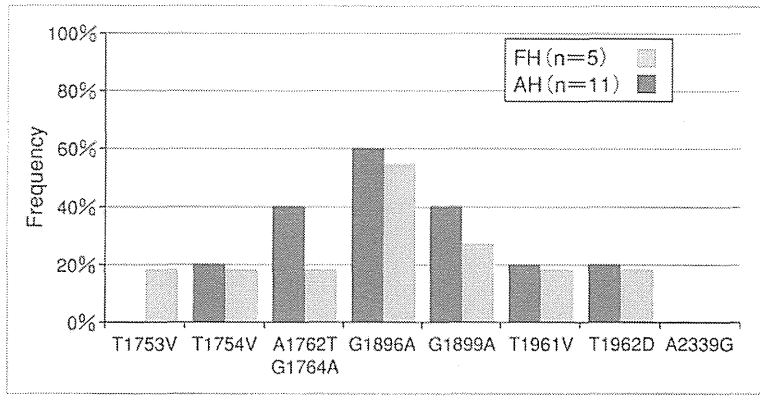

図3　*de novo*肝炎の病態でのウイルス変異の違い

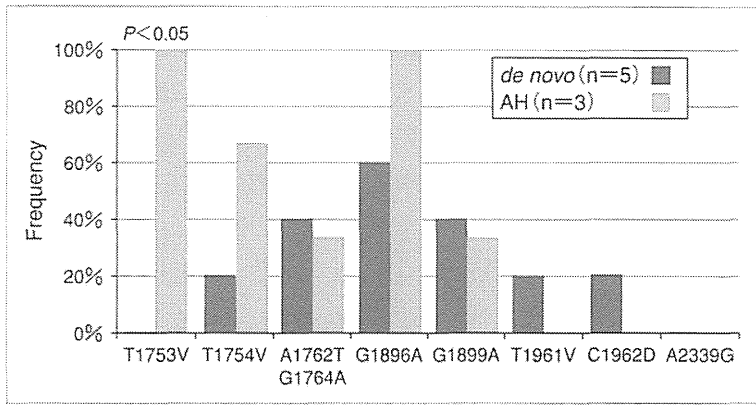

図4　劇症肝炎症例におけるウイルス変異の違い

次に，*de novo*肝炎の中で劇症化した症例とそれ以外の転帰となった症例で比較したところ有意な差は認められなかった(図3)．劇症化した症例を比較すると急性肝炎からの劇症肝炎でT1753Vが3例中3例認めるが*de novo*肝炎では5例中1例も認めず有意な差を認めた(図4)．

今回検討した9か所のウイルス変異の検討では*de novo*肝炎の発症，劇症化と関連のある変異を同定することはできなかった．症例数を増やすと同時に全塩基配列の検討を施行中である．

おわりに

肝臓専門医が主体となって，腫瘍内科，血液内科，膠原病内科などさまざまな科の先生方と連携して*de novo* B型肝炎発症の予防法，治療法を確立していく必要がある．

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Ⅱ．*de novo* B型肝炎を知る・診る・防ぐ

1．*de novo* B型肝炎の臨床的特徴

【梅村 武司・田中 榮司】

はじめに

B型肝炎ウイルス(hepatitis B virus：HBV)キャリアおよびその既往感染者では，移植(肝臓・造血幹細胞)，悪性腫瘍，リウマチ・膠原病などの治療に抗腫瘍薬，免疫抑制薬を使用すると，その使用中または使用後にHBVが再活性化して肝機能異常を起こし得る。この再活性化は臨床家であれば知らなければならない病態であり，臨床的には次の2点が問題となる。一つはHBVの再活性化に伴いB型肝炎が増悪し，重症化・劇症化して死亡する症例が存在することである。もう一つは重症肝炎に至らなくても肝機能異常が持続することにより，原疾患治療の中断もしくは中止が余儀なくされ，原疾患のコントロールが不十分となり予後が悪くなることである。

HBV再活性化のなかで，特にHBV既往感染者で起こるものを*de novo* B型肝炎と称している。この*de novo*肝炎の存在は以前から報告がされていたが，症例数が少なかったため臨床的にあまり重要視されていなかった。しかし，CD20陽性悪性リンパ腫に対する治療薬としてリツキシマブが使用されるようになると，その報告が急激に増加した。さらに，使用される生物学的製剤の種類，使用頻度が多くなったため，様々な疾患で*de novo* B型肝炎の発症に注意が喚起されるようになってきた。ここでは，わが国や海外のデータをもとに*de novo* B型肝炎の臨床的特徴を紹介する。

1 *de novo* B 型肝炎について

HBs 抗原陰性かつ HBc 抗体陽性の既往感染者は，これまでは臨床的に治癒と判断されていた人々であり，わが国では約 20 %に存在すると予測されている。通常 HBV に感染した後は非特異的な自然免疫に引き続き，ウイルス特異的な免疫反応が起こる。この時は細胞傷害性 T 細胞による細胞性免疫が重要な役割を果たしている。細胞性免疫は急性肝炎罹患後，年単位で継続するため肝臓内では感染性のあるウイルスの産生が持続するが，細胞傷害性 T 細胞の働きのため血液中へのウイルスの放出は極めて少量に抑えられている。これが既往感染と呼ばれる状態である。よって HBV に特異的な細胞傷害性 T 細胞が HBV の増殖をコントロールできないような状態に陥ると，HBV DNA が急速に増殖することになり肝炎が再燃する。これが *de novo* B 型肝炎の病態である。

抗腫瘍薬治療後に発生した *de novo* B 型肝炎をまとめた報告は，1975 年の Wands らによるものが最初である。その後，通常の抗腫瘍薬だけでなく血液疾患の移植後でも同様の検討がなされている。2001 年には，Dervite らが非ホジキンリンパ腫の治療で使用した抗 CD 20 抗体（リツキシマブ〔リツキサン®〕による *de novo* 肝炎を初めて報告した[1]。その後，リツキサン®による *de novo* 肝炎発症例の報告が多くなされるようになった。

多数例での *de novo* 肝炎の検討は，HBV 既往感染者の多いアジアから報告されている。2006 年に香港の Hui らが，悪性リンパ腫の治療を行った HBs 抗原陰性者 244 名の前向きコホート患者群で，*de novo* B 型肝炎，急性肝不全の発症率，危険因子などについて詳細な検討を発表した[2]。244 例中 8 例（3.3 %）で *de novo* 肝炎を発症しており，そのうち 3 例で急性肝不全を発症し，1 例が死亡した。*de novo* 肝炎の発症の危険因子はリツキサン®と副腎皮質ステロイドの併用療法であった。

さらに，*de novo* 肝炎は急性肝不全発症の危険因子であった。Hui らは *de novo* 肝炎の患者を詳細に検討した。臨床経過をまとめると図 1 のようになる。化学療法終了後，まず HBV DNA の増殖が起こり，それから中央値で 10 週後に

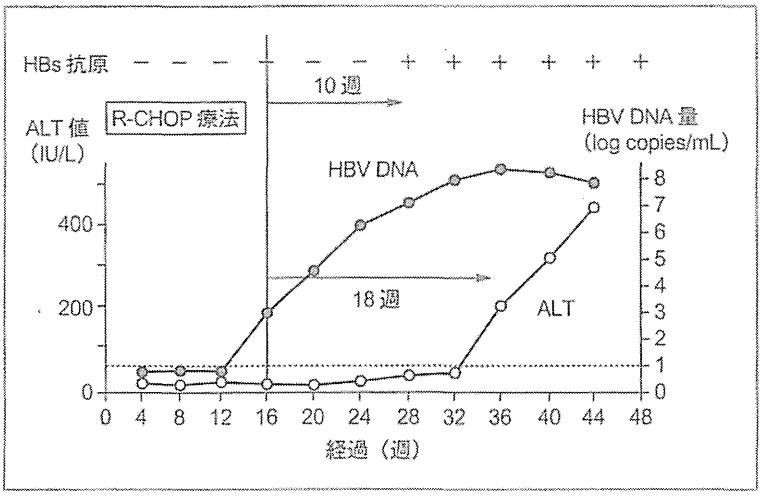

図 1　*de novo* B 型肝炎の発症パターン

de novo 肝炎でのウイルス・肝機能検査の推移。まず，HBV DNA が陽性になり，陽性後 10 週経過して HBs 抗原が陽性となり，18 週後に ALT が上昇する。
（文献 2 より改変）

HBs 抗原が陽転化する。HBV DNA 陽性化してから中央値 18 週後になると初めて ALT 値が上昇して肝炎を発症する。よって *de novo* 肝炎の予防には，HBV DNA 量の増加を認めてから核酸アナログの内服を開始することを提案している。エビデンスレベルの高い報告であるが，治療前からごく少量の HBV DNA が陽性の症例が含まれていること，治療前と再活性化時点での HBV DNA の核酸配列の相同性が低めの症例もあり，輸血等による感染などの可能性を完全には否定することはできない。

2009 年には香港の Yeo らが HBs 抗原陰性のびまん性大細胞性リンパ腫患者に CHOP 療法（シクロホスファミド〔エンドキサン®〕，アドリアマイシン〔ドキソルビシン；アドリアシン®〕，ビンクリスチン〔オンコビン®〕，プレドニゾロン〔副腎皮質ステロイド〕と R-CHOP（リツキシマブ＋ CHOP）療法を行った場合の *de novo* 肝炎の発症頻度の違いを報告した[2]。前向きに経過観察された 80 症例のうち HBc 抗体陽性者は 46 例であり，この群について CHOP 療法施行者 25

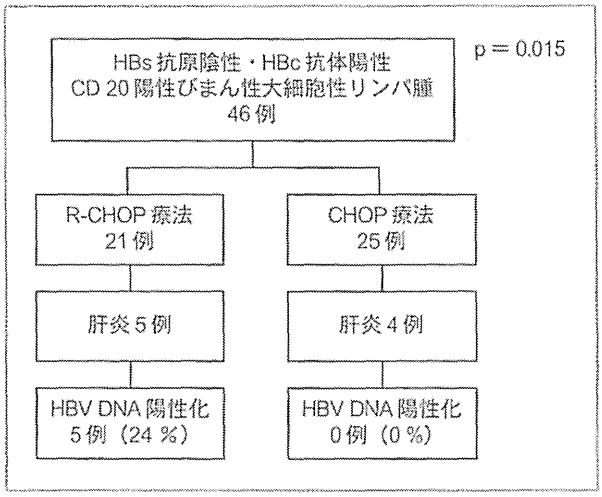

図 2　びまん性大細胞性リンパ腫患者からの HBV 再活性化の検討

CD 20 陽性びまん性大細胞性リンパ腫では，リツキサン®の含まれている R-CHOP 療法を施行した患者のみから HBV DNA が再活性化している。

（文献 3 より改変）

例と R-CHOP 療法施行者 21 例について比較検討した。CHOP 療法施行群では HBV DNA の上昇は 1 例も認めなかったが，R-CHOP 療法施行群では 24 %（21 例中 5 例）において *de novo* 肝炎の発症を認めた（図 2）。リツキサン®を含む化学療法では，*de novo* 肝炎発症のリスクが高いことが明らかである。

2 わが国における *de novo* B 型肝炎の背景

わが国では，厚生労働省の研究班で *de novo* B 型肝炎発症の全国調査を行った[4]。平成 12 ～ 16 年(2000 ～ 2004 年)の 5 年間に，新たに HBs 抗原陽性になった患者についてアンケート調査を行い，最終的には 552 例について検討を行った[5]。552 例中 529 例（96 %）が B 型急性肝炎で，23 例（4 %）が *de novo* 肝炎

であった。劇症肝炎の発症率は，*de novo* 肝炎では 23 例中 5 例（22 %）であり，急性肝炎の 529 例中 45 例（9 %）と比較して有意に高率であることが判明した。特に劇症肝炎を発症した *de novo* 肝炎の死亡率は 100 %（5 / 5）と，急性肝炎の 42 %と比較して有意に高率であった。しかも，*de novo* 肝炎を発症した症例は核酸アナログ（当時はラミブジン〔ゼフィックス®〕）がほぼ全例で投与されていたが，劇症化した症例は残念ながら全例死亡していた。つまり，*de novo* 肝炎が発症してから核酸アナログを投与しても重症例では救命することができないことがわかった。☞ サイドメモ 7

その後，平成 19 ～ 22 年（2007 ～ 2010 年）の 4 年間について，厚生労働省研究班（熊田博光 班長）で継続して *de novo* 肝炎の疫学調査を継続して行った。班員の施設において新規に経験した *de novo* 肝炎 16 例の登録があり，最初の調査の 23 例と合わせると計 39 例になる。後ろ向きではあるが，これらの症例についての臨床的背景などについて紹介する。

患者背景を表 1 に示す。発症年齢は中央値 64 歳で，男性にやや多い。背景疾患は従来の非ホジキンリンパ腫が 24 例（62 %）と最も多い。次いで，末梢血幹細胞移植後の多発性骨髄腫の症例が 8 例（21 %）で認められる。劇症肝炎を発症した症例は 11 例（28 %）であった。最初の調査の時と同様で，発症後に核酸アナログが全例投与されているにもかかわらず死亡していた。筆者らの施設でも，他院から紹介された肝不全に陥って死亡した *de novo* 肝炎症例を経験した。核酸アナログを内服開始すると HBV DNA は減少していくが，最終的には肝再

サイドメモ 7

劇症肝炎を発症した *de novo* B 型肝炎は全例死亡している

わが国のデータでは劇症肝炎を発症した *de novo* B 型肝炎の症例は，肝炎の発症後に核酸アナログ（ゼフィックス®，バラクルード® など）を全例投与されているが，残念ながら全例死亡している。よって，厚生労働省の研究班から発表されているガイドラインを遵守することが必要である。

表1　患者背景の検討

	中央値 (N＝39)	平成 12～16 年 (N＝23)	平成 19～22 年 (N＝16)	p
年　齢	64	63	66	0.091
男　性	59 %	61 %	56 %	＞0.2
非ホジキンリンパ腫	62 %	57 %	69 %	＞0.2
多発性骨髄腫	21 %	22 %	19 %	＞0.2
劇症化した症例	28 %	22 %	38 %	＞0.2
肝不全による死亡	44 %	35 %	56 %	0.16

わが国における *de novo* B 型肝炎の患者背景の検討であり，劇症化した症例，肝不全で死亡した症例はそれぞれ 28 %，44 %と高率である。平成 12～16 年度，19～22 年度における背景に差はない。

（厚生労働省研究班〔熊田博光 班長〕データより）

生が起こらず，多臓器不全となって死亡に至った。やはり劇症化した場合の救命は困難であることを実感した。

今回の解析で，背景疾患として多発性骨髄腫の割合が 20 %を占めることが判明したため，非ホジキンリンパ腫の患者と背景因子，予後などを比較した(表2)。両群で年齢と性別に差はなかったが，多発性骨髄腫の症例では 1 例も劇症化した症例はなく，肝不全による死亡例も 1 例も認めなかった。多発性骨髄腫患者に発症した *de novo* 肝炎の予後は，非ホジキンリンパ腫患者と比較すると予後が良いと考えられた。しかし急性肝不全の登録患者では，多発性骨髄腫からの劇症肝炎の発症例の報告もあるようであり，今後のデータの蓄積が必要である。

感染したウイルス側の要因についての検討も行っている。*de novo* 肝炎では，急性肝炎と比較して遺伝子型（genotype）B の比率が比較的高い傾向があったが，最近の 39 例の解析では有意差はなかった。さらに，劇症肝炎と関連性の強いプレコア変異（G1896A），コアプロモーター変異（A1762T，G1764A）についても検討を行ったが，*de novo* 肝炎の発症・劇症化症例でこれらの変異が多いと

表 2　悪性リンパ腫と多発性骨髄腫による比較検討

	悪性リンパ腫 (N＝24)	多発性骨髄腫 (N＝8)	p
年　齢	64	63	＞0.2
男　性	54 %	63 %	＞0.2
劇症化した症例	42 %	0 %	0.03
慢性化した症例	25 %	13 %	＞0.2
死亡例	50 %	50 %	＞0.2
肝不全による死亡の割合	83 %	0 %	0.003

悪性リンパ腫の患者では高率に劇症化しており，肝不全による死亡率が高い。一方，多発性骨髄腫では劇症化例はなく肝不全による死亡もなかった。

（厚生労働省研究班〔熊田博光 班長〕データより）

いう傾向は認められていない。現在これらの症例について全塩基配列の決定を行い，解析中である。

おわりに

ようやく *de novo* B 型肝炎の危険性が一般に周知されてきた状況であるが，未だに劇症肝炎からの死亡例の報告が絶えない。この肝炎は核酸アナログの予防投与や HBV DNA の定期検査で予防可能であるが，その費用対効果が問題となっている。今後の課題は，HBc 抗体陽性者が人口の約 20 %を占めるわが国での *de novo* 肝炎について，基礎疾患や治療薬の違いによる発症率の違いを明らかにし，個々に対応した予防の基準を決定していくことである。

▶ ここがポイント！

・HBV 既往感染とは HBs 抗原陰性，HBc 抗体もしくは HBs 抗体陽性の状態である。しかし，肝細胞の核内には cccDNA（covalently closed circular DNA：二本鎖閉鎖環状 DNA）の形でウイルス遺伝子は残存している。
・*de novo* B 型肝炎とは，HBV の既往感染例において免疫抑制薬や抗悪性腫瘍薬を投与することで血清 HBV DNA が検出され発症した肝炎のことである。

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Case Report

Recurrent Hepatitis B Following Recurrence of Hepatocellular Carcinoma after Living Donor Liver Transplantation

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Abstract

Hepatitis B virus (HBV) recurrence after liver transplantation for HBV-associated liver diseases results in decreased patient and graft survival. Herein we have reported two cases of HBV recurrence following relapse of hepatocellular carcinoma (HCC) after living donor liver transplantation (LDLT). Both cases had LDLT for end-stage liver disease secondary to HBV infection with nodules of HCC exceeding the Milan criteria. HBV prophylaxis using hepatitis B immunoglobulin with nucleos (t) ide analogues were given and HBV DNA levels were consistently undetectable after LDLT. HCC recurred at 5 months and 13 months posttransplant respectively, and chemotherapy and radiation therapy were performed. HBV recurrence occurred during the treatment of HCC. HBV DNA levels increased despite the treatment with anti-HBV agents after HBV recurrence. In hepatitis B surface antigen positive recipients, HBV prophylaxis should be intensified during the treatment of recurrent HCC.

Key words : Recurrence · Hepatitis B · Hepatocellular carcinoma · Living donor liver transplantation

Introduction

End-stage liver disease secondary to hepatitis B virus (HBV) is one of the major indications for liver transplantation (LT)[1)~3)]. Before the use of appropriate prophylactic treatment, posttransplant HBV recurrence was a main problem with a cumulative HBV recurrence rate of about 80%[1)]. Prophylactic use of hepatitis B immunoglobulin (HBIG) in combination with nucleoside analogue lamivudine (LAM) has markedly decreased the risk of posttransplant HBV recurrence rate, however, approximately 10% of transplanted patients develop recurrent HBV infection[4)~6)].

Chronic HBV infection remains the major cause of hepatocellular carcinoma (HCC) in the world[7)]. Although LT is an effective treatment for HCC that provides excellent oncological results as well as a cure for cirrhosis, risk estimation of posttransplant HCC recurrence is an essential

Abbreviations
HBV ; hepatitis B virus, HCC ; hepatocellular carcinoma, LDLT ; living donor liver transplantation, LT ; liver transplantation, HBIG ; hepatitis B immunoglobulin, LAM ; lamivudine, ADV ; adefovir dipivoxil, anti-HBs ; antibody to hepatitis B surface antigen, HBsAg ; hepatitis B surface antigen, PCR ; polymerase chain reaction, HBeAg ; hepatitis B e antigen, CT ; computed tomography, AFP ; alpha-fetoprotein, HBcAb ; hepatitis B core antibody, 5-FU ; 5-fluorouracil, Gy ; gray, ETV ; entecavir, DCP ; des-gamma-carboxy prothrombin, lipiodol ; iodized oil, ALT ; alanine aminotransferase

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element in selecting patients. The size of the tumor, the number of tumors, and the presence of major vessel invasion have been incorporated into the Milan criteria, which predicts a good prognosis for transplant patients with HCC[8].

Previous studies have shown that pretransplant HBV viral load and HBIG monoprophylaxis might be significant predictors of posttransplant HBV recurrence[9][10]. Recent data suggests that posttransplant HCC recurrence is also associated with HBV recurrence[11]. Herein, we report on two patients who presented with HBV recurrence following relapse of HCC after living donor liver transplantation (LDLT).

Case reports

Both patients had LDLT for end-stage liver disease secondary to HBV infection with multiple HCCs exceeding the Milan criteria. LAM and adefovir dipivoxil (ADV) were administered preoperatively and HBIG was added to them for HBV prophylaxis after the LDLT. The patients received HBIG, with an initial dose of 10,000 U during the anhepatic phase during the LDLT, followed by 5,000 U/day for 1 week after the LDLT. Thereafter, 5,000 U/day of HBIG was administered every 1 to 3 months and the antibody to hepatitis B surface antigen (anti-HBs) titers had been kept consistently above 200 IU/L.

Case 1

The patient was a 46-year-old man. Before LDLT, he had positive serum hepatitis B surface antigen (HBsAg), HBV DNA (measured by amplification using polymerase chain reaction (PCR)) (lower level of detection 2.6 log copy/mL) and hepatitis B e antigen (HBeAg). His HBV DNA titer was 3.9 log copy/mL. Abdominal computed tomography (CT) revealed nodules in segment II, V and VIII suspicious for HCC, with the maximal diameter of the tumors being 6.0 cm in segment V. At that time, his serum alpha-fetoprotein (AFP) level was 88.9 ng/mL (normal level < 6.2 ng/mL). LDLT was performed using the right lobe graft donated by his wife with positive hepatitis B core antibody (HBcAb). His immunosuppression consisted of tacrolimus, mycophenolate mofetil and corticosteroids. The posttransplant course was uneventful. The histology of the explanted liver showed a nodule of combined HCC and cholangiocellular carcinoma (6.6 x 4.3 cm) in the segment V with portal venous invasion with the presence of multiple nodules of HCC. His HBV DNA level became undetectable immediately after the LDLT, and AFP level decreased to 7.4 ng/mL 2 months after the LDLT. Thereafter, HBsAg and HBV DNA had been consistently negative, however, AFP level increased gradually. At 5 months posttransplant, abdominal CT revealed multiple metastatic lymph nodes around the aorta, and therefore, chemotherapy consisted of intravenous cisplatin, 5-fluorouracil (5-FU) and gemcitabine was introduced. A repeat abdominal CT was performed at 7 months posttransplant and the lymph nodes had grown. Therefore, chemoradiotherapy with oral S-1 (80 mg given daily, for 28 days) was initiated. Radiation therapy was administered once daily, five fractions a week at 2 gray (Gy) per fraction, with a total of 46 Gy administered over 5 weeks. At 8 months posttransplant, he demonstrated positive HBsAg during the chemoradiotherapy despite continuous HBV prophylaxis with HBIG, LAM and ADV. Immediately before HBV recurrence his anti-HBs titer was 509 IU/L and both HBsAg and HBV DNA were negative. Although combination therapy with entecavir (ETV) and ADV was started, his HBV DNA level increased thereafter. After the chemoradiotherapy, a CT scan showed the presence of multiple nodules throughout the whole liver graft and bone metastases. Finally, he died of recurrent HCC at 12 months posttransplant. The postoperative course of this patient is summarized in Figure 1A.

Case 2

The patient was a 58-year old woman. Before LDLT, she had positive HBsAg and negative HBV

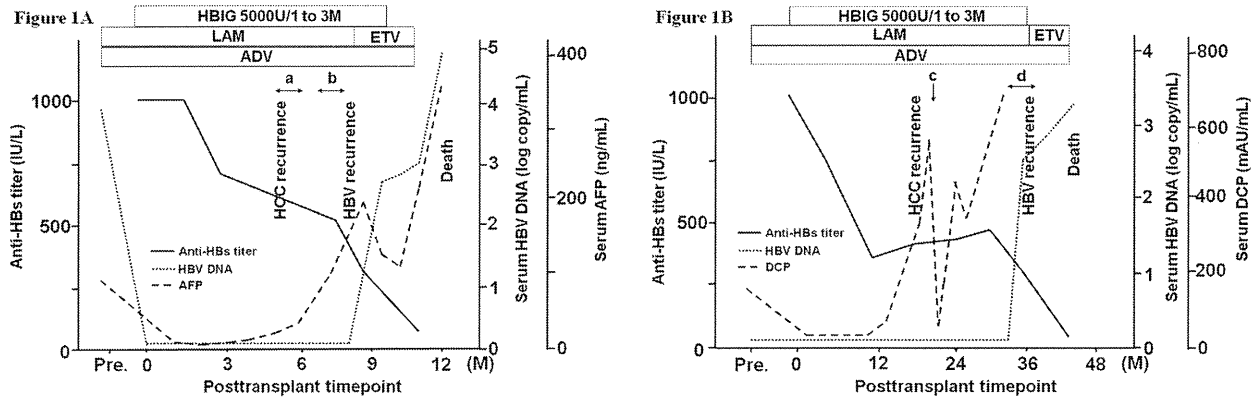

Fig. 1 Changes in serum anti-HBs titer, HBV DNA, AFP and DCP levels after LDLT. HBV recurred after relapse of HCC. (A). Case 1. a : intravenous chemotherapy. b : chemoradiotherapy with oral S-1. (B). Case 2. c : resection of lung metastasis. d : transarterial chemo-lipiodolization and radiation therapy.

DNA and HBeAg. Abdominal CT revealed multiple nodules of HCC throughout the whole liver. At that time, her serum AFP level was 2.4 ng/mL and des-gamma-carboxy prothrombin (DCP) level was 194 mAU/mL (normal level < 40 mAU/mL). LDLT was performed using the extended left lobe plus caudate lobe graft donated by her daughter with positive HBcAb. Her immunosuppression consisted of cyclosporine, mycophenolate mofetil and corticosteroids. The posttransplant course was uneventful. Her HBV DNA had been consistently negative by PCR, and DCP level decreased to 14 mAU/mL 2 months after the LDLT. At 13 months posttransplant, DCP level increased to 70 mAU/mL, and chest CT revealed a small (10 mm) nodule in the right lower lobe suspicious for metastatic disease. At 18 months posttransplant, thoracic surgery performed a video assisted thorascopic wedge resection of the metastasis in the right lung. At 30 months posttransplant, abdominal CT revealed two nodules in the liver graft invading to the inferior vena cava. Therefore, transarterial chemo-lipiodolization using a mixture of epirubicin and iodized oil (lipiodol) and radiation therapy were performed. Radiation therapy was administered once daily, five fractions a week at 2 Gy per fraction, with a total of 50 Gy administered over 5 weeks. After the therapy, she demonstrated positive HBsAg and HBV DNA at 36 months posttransplant despite continuous HBV prophylaxis with HBIG, LAM and ADV. Immediately before HBV recurrence her anti-HBs titer was 223 IU/L and both HBsAg and HBV DNA were negative. Combination therapy with ETV and ADV was started, however, her HBV DNA level increased thereafter. Although repeat CT scans showed regression of the tumors in the liver graft, multiple lung metastases were identified. She was subsequently started on sorafenib but it was ineffective. Finally, she died of recurrent HCC at 43 months posttransplant. The postoperative course of this patient is summarized in Figure 1B.

Discussion

In this report, we have shown two cases of recurrent HBV following recurrence of HCC after LDLT. Our patients received continuous HBV prophylaxis with HBIG, LAM and ADV, and their HBsAg and HBV DNA were consistently negative before HCC recurrence. Both had multiple HCCs exceeding the Milan criteria at the time of LDLT. Case 1 with a high serum AFP concentration had a large tumor with the presence of histological portal vein invasion, and Case 2 with a high serum DCP had multiple tumors throughout the whole liver. Chemotherapy and radiation therapy were performed for the treatment of HCC recurrence without any adjuvant chemotherapy after the LDLT. In our cases, HBV DNA levels increased despite combination antiviral treatment with ETV and ADV after HBV

recurrence.

HBV recurrence after LT for HBV-associated liver diseases results in decreased patient and graft survival[3]. Although combined prophylaxis with HBIG and LAM has dramatically produced excellent results, about 10% of HBsAg-positive recipients experience recurrent HBV infection[4)~6)]. Several studies have shown that high HBV viral loads at the time of transplantation are strongly associated with posttransplant HBV recurrence[9)12)]. Marzano et al suggested that serum HBV DNA titers should be below 100,000 copies/mL in order to reduce the risk of HBV recurrence[9]. In our cases, we presume that their low HBV viral loads at the LDLT did not affect the HBV recurrence.

Several mechanisms may contribute to recurrent HBV following recurrence of HCC. Antitumor chemotherapy may be important risk factor for HBV recurrence. Both immunosuppression due to chemotherapy and immunosuppressive therapy after LDLT can facilitate the replication of HBV. In previous reports, several risk factors have been proposed for reactivation of HBV during or after chemotherapy[13]. Although elevated pre-chemotherapy serum alanine aminotransferase (ALT) and HBV DNA load have been reported to be associated with developing reactivation[14], our patients had normal ALT and undetectable HBV DNA levels. Case 1 presented with recurrent HBV infection after the chemoradiotherapy with oral S-1 following chemotherapy consisted of intravenous cisplatin, 5-FU and gemcitabine. In Case 2, HBV recurrence occurred after the transarterial chemo-lipiodolization using a mixture of epirubicin and lipiodol and radiation therapy. Yeo et al have reported systemic chemotherapy for HCC has been associated with HBV reactivation in HBs-Ag positive patients[15]. Jang JW et al have shown that transarterial chemo-lipiodolization was also a risk for HBV reactivation[16]. Moreover, in a recent study, radiation therapy has been demonstrated to induce HBV reactivation caused by the release of IL-6[17].

Recently, we reported 3 recurrent HBV patients after LDLT for liver cirrhosis due to HBV, and one of the patients had HCC at the time of LDLT without HCC recurrence after the LDLT[18]. All the patients were treated with LAM and ADV, and their HBV DNA were consistently negative after HBV recurrence. On the other hand, in this report, both HBV DNA levels increased after HBV recurrence despite the continuous treatment with ETV and ADV. Faria et al have shown that HCC recurrence itself is associated with HBV recurrence, because HBV replication in HCC cells may act as a viral source[11]. Therefore, we presume that rapid HCC progression had effect on the increasing HBV DNA levels in our patients after HBV recurrence. In addition, their anti-HBs titers gradually decreased despite the intravenous HBIG administration, possibly because viral production in the recurrent HCC might increase HBIG consumption. In some situations, prevention of HCC recurrence may help reduce the risk of HBV recurrence after LT. Pretransplant transarterial embolization and reduced immunosuppression after LT have recently been shown to decrease the risk of HCC recurrence[19)20)]. However, further studies are needed to develop effective strategies to prevent posttransplant HCC recurrence.

In this report, our patients developed recurrent HBV after relapse of HCC, and their HBV DNA levels increased despite the treatment with anti-HBV agents. In HBsAg-positive recipients, it is possible that severe and progressive recurrent HBV may occur following HCC recurrence, and therefore, HBV prophylaxis should be intensified during the treatment of recurrent HCC.

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生体肝移植後肝細胞癌再発後の慢性B型肝炎の再発

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肝移植後のB型肝炎の再発は移植成績を低下させる．生体肝移植後に肝細胞癌再発を認め，その後B型肝炎の再発を認めた2例を経験したので報告する．いずれもミラノ基準を超えた肝細胞癌とB型肝炎による非代償性肝硬変に対する生体肝移植後であった．B型肝炎に対する免疫グロブリンと核酸アナログが投与され，B型肝炎の再発予防が行われ，いずれも血中のB型肝炎は検出できないレベルでコントロールされていた．肝細胞癌はそれぞれ移植後5ヶ月，13ヶ月後に再発し，放射線療法と化学療法が施行された．抗ウイルス療法にもかかわらず，再発肝細胞癌に対する治療中にB型肝炎のDNAレベルは上昇した．HBs抗原陽性のレシピエントにおいては再発肝細胞癌の治療の間，B型肝炎再発予防を十分注意しながら行う必要がある．

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Impact of Conversion From Pegylated Interferon-α2b to Interferon-α2a for Treating Recurrent Hepatitis C After Liver Transplantation

The clinical outcomes of conversion from pegylated (peg) interferon (IFN)-α2b to peg-IFN-α2a therapy in combination with ribavirin for recurrent hepatitis C after liver transplantation (LT) have not been reported (*1–3*).

Living-donor liver transplantation (LDLT) was performed in 156 patients for hepatitis C at Kyushu University. Of these, 103 received peg-IFN-α2b and ribavirin and 22 patients underwent conversion from peg-IFN-α2b to peg-IFN-α2b. Indications for conversion included (a) no response (NR; n=14) to peg-IFN-α2b, (b) relapse after viral response (VR; n=5) following completing peg-IFN-α2b therapy, and (c) to prevent relapse (n=3) for VR during peg-IFN-α2b and ribavirin therapy. Splenectomy was performed in 47 (95.9%) recipients to prevent pancytopenia associated with antiviral therapy (*4*). The immunosuppression was induced with triple therapy of tacrolimus or cyclosporine with mycophenolate mofetil and steroids (*5*).

Peg-IFN-α2b with ribavirin (Pegintron with Rebetol; Merck & Co., Whitehouse Station, NJ) was used as the primary treatment for recurrent hepatitis C after LDLT. Peg-IFN-α2b was started at the dose of 0.5–1.0 μg/kg per week with 200–400 mg per day of ribavirin. The doses were escalated in a stepwise manner up to 1.5 μg/kg per week and 800 mg per day. Peg-IFN-α2a with ribavirin (Pegasys with Copegus; Chugai Pharmaceutical, Chuo-ku, Tokyo, Japan) was primarily used for patients with NR or relapse during treatment with peg-IFN-α2b with ribavirin. Peg-IFN-α2a was started at the dose of 90–120 μg per week with 200–400 mg per day of ribavirin. The doses were escalated in a stepwise manner up to 180 μg per week and 800 mg per day. The serum hepatitis C virus (HCV)-RNA level was determined by a real-time HCV assay (Accu-Gene HCV; Abbott Molecular, Des Plaines, IL) and IL28B genotyping was performed using TaqMan GTXpress Master Mix (Life Technologies, Tokyo, Japan). Peg-IFN-induced immune-mediated graft dysfunction (peg-IGD) was defined as the Levitsky et al. (*6*) did. Values are expressed as mean±standard deviation. Variables were analyzed using χ^2 tests for categorical values or the Mann–Whitney test for continuous variables. Values of $P<0.05$ were considered statistically significant.

The characteristics of the patients who underwent conversion from peg-IFN-α2b to peg-IFN-α2a antiviral treatment are described in Table 1. The outcomes of conversion from peg-IFN-α2b to peg-IFN-α2a antiviral treatment are summarized in Figure 1. Among the 14 patients with NR following peg-IFN-α2b with ribavirin therapy, 6 patients achieved VR and 3 had sustained VR (SVR) after conversion. Among the five patients with viral relapse following peg-IFN-α2b–based therapy, four patients achieved VR after conversion. Among the three patients with conversion during

TABLE 1. Patient characteristics

Variables	Values
Recipient age, yr	51.4±8.6 (54.5)
Recipient gender, male	15 (68.2)
Donor age, yr	35.7±11.3 (34.5)
Donor gender, male	16 (72.7)
Left lobe graft	13 (59.7)
GV/SLV (%)	41.4±6.4 (40.4)
Splenectomy	17 (77.3)
Tacrolimus	12 (54.5)
Mycophenolate mofetil	20 (54.5)
Steroid free	5 (22.7)
HCV-RNA titer at LDLT, log IU/mL	5.5±0.6 (5.7)
IFN before LDLT	9 (40.9)
HCV genotype 1b, 2a, and 2b	16 (72.7), 5 (22.7), and 1 (4.6)
Donor rs8099917 genotype, T/T	7 (31.8)
Recipient rs8099917 genotype, T/T	8 (36.4)
Time from LDLT to peg-IFN-a2b, mo	14.3±18.2 (8.1)
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3 (1.0)
Ribavirin dose peg-IFN-a2b, mg/kg/d	6.1±2.9 (6.2)
Duration of peg-IFN-a2b treatment, mo	12.1±14.2 (10.7)
HCV-RNA titer at conversion, log IU/mL	4.1±2.6 (4.9)
Peg-IFN-a2a dose, mg/kg/wk	2.1±0.8 (1.9)
Ribavirin dose with peg-IFN-a2a, mg/kg/d	3.5±4.3 (2.1)
Duration of peg-IFN-a2a treatment, mo	14.2±10.1 (9.8)
VR with peg-IFN-a2b	8 (36.4)

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; VR, viral response.

VR by peg-IFN-α2b–based therapy, two patients achieved SVR. However, all three patients with conversion during VR by peg-IFN-α2b–based therapy had peg-IGD, including de novo autoimmune hepatitis (n=2) and chronic rejection (n=1), resulting in graft loss in two patients.

The viral status after peg-IFN conversion is summarized in Table 2. Among patients with NR, relapse after VR, HCV-RNA seropositivity, and VR following peg-IFN-α2b, the rates of VR after converting to peg-IFN-α2a were 42.8%, 100.0%, 57.9%, and 100.0%, respectively. The rates of SVR were 21.4%, 80.0%, 36.8%, and 40.9%, respectively.

Univariate analysis was performed to identify factors associated with VR after conversion from peg-IFN-α2a to peg-IFN-α2b. In this analysis, only history of VR during peg-IFN-α2a with ribavirin treatment (57.1% vs. 0.0%; P=0.02) was significantly associated with VR after conversion (Table 3). By contrast, low HCV-RNA titer at conversion (1.8±1.9 vs. 5.3±2.0 log IU/mL; P<0.01) and history of VR during peg-IFN-α2a with ribavirin treatment (66.7% vs. 14.3%; P=0.03) were significantly associated with SVR after conversion (Table 4).

The major structural difference between peg-IFN-α2b and peg-IFN-α2a is the conjugated polyethylene glycol (*7–10*). Peg-IFN-α2b (12 kDa) has a single-branched polyethylene glycol, whereas peg-IFN-α2a (40 kDa) has bulky multiple branched conjugates. Consequently, peg-IFN-α2a has a smaller distribution volume (10 vs. 40 L), longer absorption half-life (50 vs. 4.6 hr), and longer elimination half-life (80 vs. 40 hr). Moreover, it was reported that the serum concentration of peg-IFN-α2a was 20 mg/mL at 7 days after injection compared with almost zero for peg-IFN-α2b (*8*).

As a posttransplantation primary antiviral agent for recurrent hepatitis C, peg-IFN-α2a was used in very limited series, and peg-IFN-α2b has become the most widely used and studied regimen for use after LT (*11–13*). Among them, Dinges et al. (*14*) only reported the actual rate of SVR (47%) following peg-IFN-α2a with ribavirin for 19 patients after LT, whereas dose

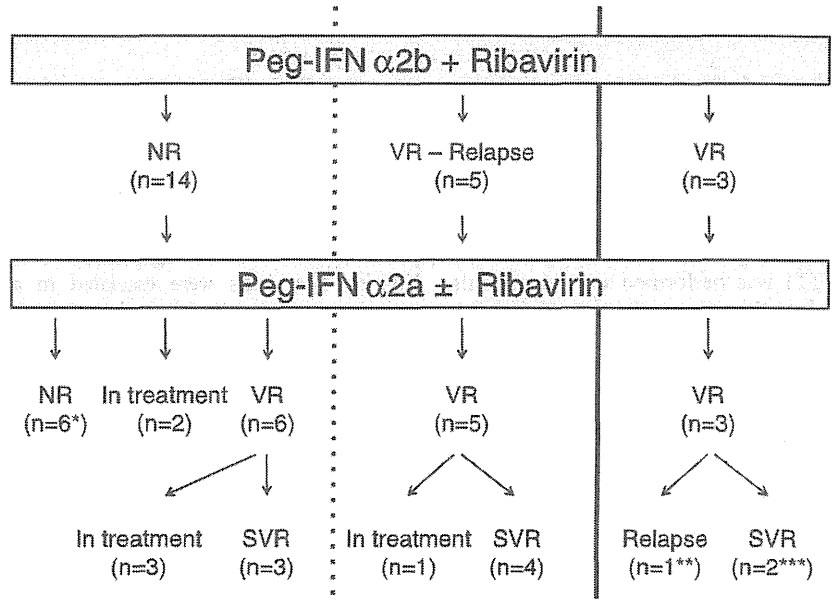

FIGURE 1. Twenty-two patients who received peg-IFN-α2b with ribavirin were converted to peg-IFN-α2a with or without ribavirin. *AIH (n=1); **AIH (n=1); ***AIH (n=1) and CR (n=1). AIH, autoimmune hepatitis; CR, chronic rejection; IFN, interferon; NR, no response; peg, pegylated; SVR, sustained viral response; VR, viral response.

TABLE 2. Viral status after conversion from peg-IFN-α2b to peg-IFN-α2a antiviral therapy

Response to peg-IFN-α2b	VR for peg-IFN-α2a (%)	SVR for peg-IFN-α2a (%)
NR	6/14 (42.8)	3/14 (21.4)
Relapse after VR	5/5 (100.0)	4/5 (80.0)
Positive HCV-RNA	11/19 (57.9)	7/19 (36.8)
VR	3/3 (100.0)	2/3 (67.7)
Total	14/22 (63.6)	9/22 (40.9)

HCV, hepatitis C virus; IFN, interferon; NR, no response: peg, pegylated; SVR, sustained viral response; VR, viral response.

modification was necessary in 26% of patients. Although their study was small and nonrandomized, the rate of SVR was superior to that achieved by peg-IFN-α2b with ribavirin (~30%) (*15*).

Restarting peg-IFN-α2a with ribavirin in nontransplantation settings after a poor response to previous IFN therapy has been reported in a few studies (*16–18*). Jensen et al. (*16*) conducted a randomized trial in which treatment was restarted in 950 patients who did not respond to prior peg-IFN-α2b with ribavirin therapy. In that study, the rate of SVR after 72 weeks of peg-IFN-α2a with ribavirin treatment was 16%. Herrine et al. (*17*) randomized 124 patients with poor response to peg-IFN-α2b with ribavirin therapy. In that study, 37% of patients had SVR after conversion to peg-IFN-α2a with ribavirin. Therefore, we think that the 21.4% of SVR rate after conversion from peg-IFN-α2b to IFN-α2a is fairly acceptable.

However, the main adverse outcome of conversion to peg-IFN-α2a is peg-IGD, a concept recently proposed by Levitsky et al. (*6*). It was reported that IFN could lead to IGD, which may include acute rejection, chronic rejection, and autoimmune hepatitis as well as graft loss (*15, 19, 20*). They reported that

TABLE 3. Predictors for VR after conversion from peg-IFN-α2b to peg-IFN-α2a

Variables	VR		*P*
	No (n=6)	Yes (n=14)	
Recipient age, yr	58.8±5.1	51.4±8.6	0.85
Recipient gender, male	3 (50.0)	11 (78.6)	0.20
Donor age, yr	32.5±11.1	34.5±9.5	0.68
Donor gender, male	3 (50.0)	11 (78.6)	0.20
Left lobe graft	3 (50.0)	8 (57.1)	0.77
GV/SLV, %	41.7±4.7	41.1±7.6	0.84
Splenectomy	4 (66.7)	11 (78.6)	0.57
Tacrolimus	4 (66.7)	6 (42.6)	0.33
Mycophenolate mofetil	6 (100.0)	12 (85.7)	0.33
Steroid free	2 (33.3)	3 (21.4)	0.57
HCV-RNA titer at LDLT, log IU/mL	5.7±0.2	5.6±0.6	0.67
IFN before LDLT	2 (33.3)	6 (42.9)	0.69
HCV genotype 1b, 2a, and 2b	6 (100.0)	9 (64.3)	0.09
Donor rs8099917 genotype, T/T	3 (50.0)	11 (78.6)	0.20
Recipient rs8099917 genotype, T/T	3 (50.0)	9 (64.3)	0.55
Time from LDLT to peg-IFN-a2b, mo	12.1±18.5	16.0±19.6	0.67
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3	1.0±0.3	0.35
Ribavirin dose, with peg-IFN-a2b, mg/kg/d	6.6±3.8	5.6±2.8	0.77
Duration of peg-IFN-a2b treatment, mo	20.8±24.8	8.9±5.6	0.52
HCV-RNA titer at conversion, log IU/mL	4.7±2.8	3.5±2.6	0.34
Peg-IFN-a2a dose, mg/kg/wk	2.2±0.8	1.9±0.8	0.51
Ribavirin dose, with peg-IFN-a2a, mg/kg/d	3.3±5.4	2.8±3.3	0.81
Duration of peg-IFN-a2a treatment, mo	26.7±16.2	12.9±10.5	0.06
VR with peg-IFN-a2b	0 (0.0)	8 (57.1)	0.02

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; VR, viral response.

TABLE 4. Predictors for SVR after conversion from peg-IFN-α2b to peg-IFN-α2a

Variables	SVR		P
	No (n=7)	Yes (n=9)	
Recipient age, yr	55.9±6.1	51.7±9.1	0.21
Recipient gender, male	4 (57.1)	7 (77.8)	0.38
Donor age, yr	33.7±12.1	39.0±9.5	0.30
Donor gender, male	3 (42.8)	8 (88.9)	0.06
Left lobe graft	4 (57.1)	5 (55.6)	0.95
GV/SLV (%)	42.6±5.5	39.2±7.7	0.24
Splenectomy	5 (71.4)	6 (66.7)	0.84
Tacrolimus	5 (71.4)	4 (44.4)	0.28
Mycophenolate mofetil	7 (100.0)	6 (66.7)	0.69
Steroid free	3 (42.8)	2 (22.2)	0.38
HCV-RNA titer at LDLT, log IU/mL	5.6±0.5	5.4±0.7	0.57
IFN before LDLT	2 (28.5)	4 (44.4)	0.51
HCV genotype 1b, 2a, 2b	7 (100.0)	6 (66.7)	0.09
Donor rs8099917 genotype, T/T	4 (57.1)	8 (88.9)	0.14
Recipient rs8099917 genotype, T/T	4 (57.1)	6 (66.7)	0.69
Time from LDLT to peg-IFN-a2b, mo	10.3±12.5	21.6±24.8	0.17
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3	1.0±0.3	0.35
Ribavirin dose, with peg-IFN-a2b, mg/kg/d	6.0±3.7	5.7±3.1	0.84
Duration of peg-IFN-a2b treatment, mo	12.7±17.6	11.1±5.4	0.78
HCV-RNA titer at conversion, log IU/mL	5.3±2.0	1.8±1.9	<0.01
Peg-IFN-a2a dose, mg/kg/wk	2.0±0.8	1.5±0.5	0.13
Ribavirin dose, with peg-IFN-a2a, mg/kg/d	3.2±5.0	2.6±3.2	0.79
Duration of peg-IFN-a2a treatment, mo	26.7±16.2	16.3±12.1	0.23
VR with peg-IFN-a2b	1 (14.3)	6 (66.7)	0.03

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; SVR, sustained viral response; VR, viral response.

7.2% of patients treated with peg-IFN develop peg-IGD over 10 years, with a significantly higher mortality rate. Additionally, the use of peg-IFN-α2a (odds ratio=4.7) was a significant risk factor for this event (6). In the current series, peg-IGD occurred in all three patients who converted from peg-IFN-α2b to peg-IFN-α2a, with graft loss in two patients.

In conclusion, conversion to peg-IFN-α2a–based antiviral therapy for recurrent hepatitis C after LT is a safe option, with increased VR and SVR rate, only for patients with NR or relapse on previous peg-IFN-α2b therapy.

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