厚生労働科学研究費補助金（エイズ対策研究事業）
分担研究報告書
HIV・HCV 重複感染患者の長期予後

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研究要旨　HIV・HCV 重複感染者の長期予後について

HIV・HCV 重複感染者 123 名の長期予後の調査を行った。123 名中 15 名（12%）で HCV の自然消失を認めた。一方で肝細胞癌への進展を 7 名（6%）に、非代償期肝硬変所見を 10 名（8%）に認めた。肝細胞癌あるいは肝硬変への進展は 24 名（20%）に認めた。観察期間中に 17 名（14%）が死亡しており、7 名は肝疾患関連死であった。インターフェロンを含む抗 HCV 療法は 63 名（51%）に行われ、ウイルス排除は 35 名（56%）で得られた。APRI の改善は 8 名、増悪は 3 名で認められた。HIV・HCV 重複感染者の予後改善には抗 HCV 療法は重要であるが、肝硬変・肝細胞癌への進展阻止は十分ではなく、治療法の改善が必要と考えられた。

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A. 研究目的

HIV 感染者が HCV 感染症を合併した場合、肝線維化の進展が速く、肝細胞癌の合併も若年で起こりやすい。特に患者の多くが HCV に感染している血友病の症例では大きな問題となっている。肝移植待機の順位のスコアをつける際にもこのことが問題となっている。

本研究では、(1) HIV・HCV 重複感染者において非代償性肝硬変あるいは肝細胞癌などの End Stage Liver Disease を合併する割合とその特徴、(2) HIV・HCV 重複感染者の肝病変の進展速度と進行を早める要因、を解析することを目的とした。

B. 研究方法

厚労省科学研究エイズ対策研究事業「HIV 感染症に合併する肝疾患に関する研究」班（小池和彦班長）にて平成 15 年度から平成 16 年度にかけて行われた調査により、約 200 例の HIV・HCV 重複感染者の臨床検査成績・抗ウイルス療法・合併症に関するデータの収集が行われた（小池和彦　HIV 感染症に合併する各種疾病に関する研究．厚生労働科学研究費補助金エイズ対策研究事業　平成 19 年度総括・分担研究報告書.）。この調査では初診時と 2004 年時点でのデータが収集されており、肝病変の進展が評価されている。

2014 年から 2015 年にかけてこの研究に参加した患者の追跡調査が行われている。本研究はその調査結果の解析により、研究目的に記載した項目に関する検討を行った。対象としては APRI index を観察開始から終了まで計算可能な症例 116 例（男性 112 例、女性 4 例）を対象とした。

（倫理面への配慮）

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C. 研究結果

（1）対象患者の基礎情報

男性 119 名の観察開始時平均年齢は 40 歳、平均観察期間は 156 ヶ月であった。女性 4 名の観察開始時平均年齢は 48 歳、平均観察期間は 86 ヶ月であった。

HIV 感染症の感染経路は男性では血液製剤 103 名、性交渉 13 名（MSM8 名、Heterosexual 5 名）、IV dug user 1 名、その他 2 名であった。女性では血液製剤 2 名、性交渉（heterosexual）2 名であった。

初診時のウイルス量は高ウイルス量（HCV probe >1.0 Meq/L あるいは Amplicor Momitor >100 KIU/mL）58 名（男性 55 名、女性 3 名）、低ウイルス量 7 名（いずれも男性）、陰性 10 名（男性 9 名、女性 1 名）であった。

（2）HCV の推移

①治療歴がないにもかかわらず HCVRNA が初診時から陰性であった者、あるいは経過中に自然消失した者は 15 名（男性 14 名、女性 1 名）、②治療歴がなく、HCVRNA が持続陽性の者は 34 名（いずれも男性）、③治療によって HCV RNA が消失した者は 35 名（男性 33 名、女性 2 名）、④治療したにもかかわらず治癒していない者は 28 名（男性 27 名、女性 1 名）であった。

（3）肝線維化の推移

観察開始時点で APRI が 2.0 以上で進展した線維化があると推定可能な例が 11 名（いずれも男性）あった。このうち 5 名は抗 HCV 療法による HCV 排除後に APRI が低下し、線維化が退縮した可能性があると考えられた。1 例では APRI が 1 台まで低下したものの腹水の出現を認めた。残り 5 例のうち 3 例で肝細胞癌、1 例で食道静脈瘤の新規出現を認めた。

最終経過観察地点で APRI が 2.0 以上の例は 26 例あり、このうち 21 例は経過中に APRI が 2.0 以上に上昇した症例であった。このうち 1 例に肝細胞癌、3 例に腹水・脳症、4 例に食道静脈瘤の出現を認めた。

（4）HCV 排除の効果

抗ウイルス療法により HCV が排除できたのは 35 名であるが、このうち HCV 排除後に発癌を認めたのは 2 名であった。このうち 1 名は最初から線維化の進展していた症例、もう 1 名はウイルス排除後も APRI が徐々に上昇していた症例であった。HCV 排除後も APRI の上昇を別の 3 名にも認めた。うち 1 名は腹水・脳症の合併が認められた。一方 APRI の低下を 8 名に認めた。

（5）合併症

肝細胞癌の合併は 7 名（発症平均年齢 59 歳）、腹水・脳症の合併は 10 名、これらのいずれかの合併は 15 名に認めた。いずれも男性であった。この 15 名以外にも食道静脈瘤の出現を 9 例に認めた。これらイベントの発生年齢は平均 53 歳であった。

24 名中 4 例（肝細胞癌 2 例、食道静脈雄＋腹水／脳症 1 名、食道静脈瘤 1 名）は APRI が経過を通じて 2 未満の例であった。これらの例はいずれも抗 HIV 療法が行われていたが、ddI, d4T など非硬変性門脈圧亢進症をきたす薬の使用歴は認められなかった。

期間中 17 名が死亡した。死因は肝硬変 5 名、PML3 名、肝細胞癌 2 名、多臓器不全 2 名、腎不全・肺炎・乳酸アシドーシス・リンパ腫・直腸癌各 1 名であった。

D. 考察

HIV・HCV 重複感染者のほとんどは抗レトロウイルス療法が導入され、免疫不全はコントロールされるようになってきた。最近は肝疾患、心疾患、指標疾患以外の悪性腫瘍などが生命予後を決める因子となってきている。

HIV・HCV 重複感染者では HCV の自然消失を見る例があることがこれまでも報告されているが、今回の検討では 123 例中 15 名（12%）に消失を認めた。性交渉による感染者などでは感染したウイルス量が少ないためウイルスが消失しやすいなどの理由が考えられるが、検討が必要である。

HIV・HCV 重複感染者では HCV 単独感染者に比較して肝線維化が進展しやすいことがわかっている。本検討では肝細胞癌の発生、腹水／脳症の出現、食道静脈瘤の出現を 24 名（20%）に認め、その出現年齢は平均 53 歳であった。これは HCV 単独感染

例に比べ若い傾向にある。観察期間中に５名の肝不全死が見られ、肝細胞癌による死亡よりも多い点も注目される。

観察期間中に 17 名（14%）が死亡しており、7 名は肝疾患関連死である。また、17 名中肝硬変・肝細胞癌の合併のない者は 4 例のみであり、死亡につながる合併症の発症にも肝疾患が影響を及ぼしている可能性がある。肝病態の進展防止は HIV・HCV 重複感染者の生命予後を改善する上で極めて重要と考えられる。

インターフェロンを含む抗ウイルス療法は 63 例（51%）に行われ、ウイルス排除が可能だったのは 63 例中 35 名（56%）であった。APRI の低下は 8 名、APRI の上昇は 3 名に認めており、インターフェロンによるウイルス排除にもかかわらず線維化の進展する症例もあることがわかった。今後さらに解析が必要である。

E. 結論

HIV・HCV 重複感染者では①HCV の自然消失を 12%に、②肝硬変・肝細胞癌への進展を 20%に、③肝疾患による死亡を 6%に認めた。肝病態の進展防止は HIV・HCV 重複感染者の生命予後を改善する上で極めて重要と考えられるが、そのためにはインターフェロンを含む抗 HCV 療法だけでは不十分であり、新たなオプションが必要であると考えられた。

F. 健康危険情報

なし

G. 研究発表

１．論文発表

特になし

２．学会発表

特になし

H. 知的財産権の出願・登録状況（予定を含む。）

１．特許取得

特になし

２．実用新案登録

特になし

３．その他

特になし

III. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

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Short Communication

The First Case of Deceased Donor Liver Transplantation for a Patient with End-Stage Liver Cirrhosis Due to Human Immunodeficiency Virus and Hepatitis C Virus Coinfection in Japan

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SUMMARY: We previously reported that progression of liver cirrhosis is quicker and survival is dismal in patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection, especially when acquired in childhood through contaminated blood products. Recently, we performed the first deceased donor liver transplantation (DDLT) for an HIV/HCV-coinfected hemophilic patient in Japan. A 40-year-old man was referred to our hospital for liver transplantation. Regular DDLT was performed using the piggyback technique with a full-sized liver graft. Cold ischemia time was 465 min, and the graft liver weighed 1,590 g. The antiretroviral therapy (ART) was switched from darunavir/ritonavir to raltegravir before the transplant for flexible usage of calcineurin inhibitors postoperatively; tenofovir was used as the baseline treatment. The postoperative course was uneventful, and the patient was discharged home on day 43. He started receiving anti-HCV treatment on day 110 with pegylated interferon, ribavirin, and simeprevir after the DDLT. Herein, we report the first case of DDLT in Japan. Meticulous management of ART and clotting factors could lead to the success of DDLT.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection after the use of HIV/HCV-contaminated imported blood products for hemophilia patients in the 1980s has led to increased mortality rates due to end-stage liver disease resulting from chronic hepatitis C infection (1,2). In the meantime, the development of antiretroviral agents made it possible to nearly eliminate HIV-related morbidity and mortality (3). Therefore, an urgent need has developed to establish a system to salvage those patients with HIV/HCV coinfection. It is important to note that these patients usually develop end-stage liver cirrhosis at a young age, such as in their 30s and 40s. They may also develop hepatocellular carcinoma (4,5).

In Japan, the Tokyo University group has made an intense effort to salvage those patients undergoing living donor liver transplantation (LDLT) and to yield a good survival rate after LDLT (6). However, liver transplantation from a deceased donor has not been performed thus far. In the world literature, there have been some case series of deceased donor liver transplantation (DDLT) in patients with HIV infection (7); however, an optimal antiretroviral therapy (ART) regimen and anti-HCV treatment has not been clarified yet. Herein, we report the first case of DDLT for an HIV/HCV coinfected hemophilic patient, with special consideration for antiretroviral conversion and immunosuppressive agent selection.

The patient was a 40-year-old man who was infected with HIV and HCV through imported contaminated blood products used for treating hemophilia when he was an infant. He received treatment with antiretroviral agents, and the HIV RNA levels remained under the detectable range. However, chronic hepatitis with HCV infection persisted, and he recently developed cirrhosis. Pegylated-IFN therapy combined with ribavirin was discontinued owing to mental depression, which was induced by the pegylated-IFN. He was also treated for esophageal varices with endoscopic variceal ligation. A computer tomography scan showed a relatively hypertrophic left lobe of the cirrhotic liver with ascites.

The inferior vena cava was completely surrounded by the enlarged caudate lobe of the liver. No tumor formation was noted inside or outside of the liver. The patient's Child-Pugh status was class C with 10 points and the Model for End-Stage Liver Disease score was 19 points. To HIV RNA level was below detection limits and his absolute CD4 number was around 150. However, the patient had a high HCV RNA titer. A clotting profile indicated that he had hemophilia A with a low factor VIII level, which necessitated administration of factor VIII 3 times per week. Finally, he was indicated for liver transplantation (LT) and waited 3 years with low points. However, over the 3 years his liver function progressively deteriorated. He obtained extra points on the waiting list because the mortality of HIV/HCV coinfected patients without LT is higher than that of HCV-mono-infected patients. Before LT, his ART was changed from darunavir/ritonavir to raltegravir in order to exercise flexible control of the calcineurin inhibitor. Tenofovir was used as the basic ART.

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An ABO blood type-identical liver was finally offered and an orthotopic transplantation was performed. The cold ischemic time was 465 min and the graft weight was 1,590 g. The weight of the explanted liver was 836 g. The piggyback procedure was performed, with a blood loss of 16,500 ml. The duration of the operation was approximately 705 min, mainly because of disturbed clotting profile as well as difficulty obtaining complete hemostasis owing to the patient's hemophilic status. Splenectomy was also performed as a result of a low platelet count ($<50,000/\mu l$) and possible postoperative need for interferon or other anti-HCV drugs. Owing to the difficulty of achieving complete hemostasis, our strategy was to finally perform gauze packing and removal, on postoperative day (POD) 3. After the depacking, the postoperative course was rather uneventful and without any severe infectious complications.

Histological examination revealed marked variation in the size and shape of the hepatic nodules, known as mixed micro- and macro-nodular cirrhosis. Persistent active inflammation with lymphoid follicles and interface activity was observed in the portal tract and in the thick fibrous septa. There was no evidence of hepatocellular carcinoma. With regards to immunosuppression, we tried to avoid a steroid bolus in order to prevent infectious complications due to the nature of the HIV disease and HCV flares. Anti-CD25 antibody was administered on POD 1 and 4, and tacrolimus was administered on POD 2, followed by aiming the trough level around POD 8 with steroid tapering (Fig. 1). On POD 7, ART was resumed and continued thereafter. The patient's CD4 count was preserved and even elevated owing to the splenectomy. The postoperative course of the patient was uneventful and he was discharged home on day 44 after the DDLT. He was administered the same dose and type of ART as before the DDLT. Anti-HCV treatment with combination of pegylated-interferon, ribavirin, and simeprevir was initiated on day 110 after the DDLT.

However, a sustained viral response was not achieved, and therefore, we initiated treatment with a new direct-acting antiviral agent anti-HCV drugs (DAA), sofosbuvir. The definitive outcomes of the antiviral treatment will be evaluated in the future.

We changed the ART from darunavir/ritonavir to raltegravir before LT for this purpose, which made it possible for us to use regular immunosuppressive agents (8). HIV RNA level has been undetectable throughout the observation period. Before the advent of raltegravir, most ART drugs, non-nucleoside reverse transcriptase inhibitors or protease inhibitors, interacted with immunosuppressive agents such as tacrolimus or cyclosporine because they are all metabolized by the same cytochrome P450 family (CYP3A4). Regarding the CD4

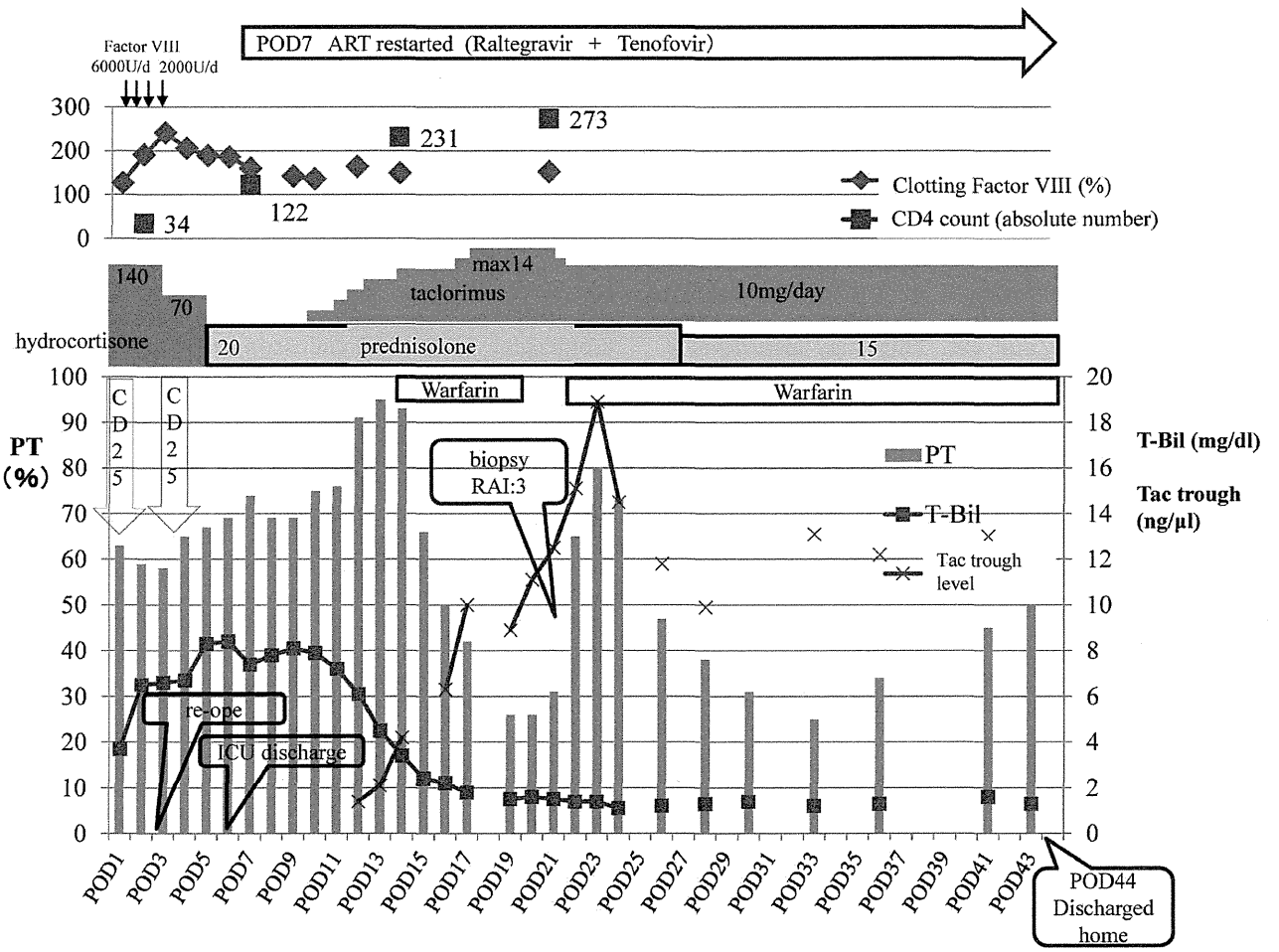

Fig. 1. Post-transplant course in a hemophilic patient with HIV/HCV co-infection. ART restarted (raltegravir, tenofovir) on day 7 and tacloriums on day 11 after the DDLT.

count, our indication for LT was a level above 100, owing to the hypersplenism due to severe portal hypertension. Immediately after the DDLT, the CD4 count dropped below 100, although it recovered spontaneously with the aid of a splenectomy, which was scheduled before the DDLT was performed (9). We believe that if the HIV titer is under control with ART, the absolute CD4 number for indication of LT could be lowered to 100, but not 200 because hypersplenism can mask the real immunological function of those patients with HIV/HCV coinfection. Also, splenectomy may increase the CD4 count and strengthen the immune function before or during LT. According to the article by Nomura et al., after splenectomy, the ratio of CD4 cells in peripheral blood decreases leading to a significant decrease in the CD4/CD8 ratio in patients with liver cirrhosis (10). Therefore, a splenectomy may not significantly increase the CD4 count before LT. However, Hashimoto et al. reported that the CD4 function, in terms of IFN-gamma production and CD4 proliferation, increased after splenectomy (11). Accordingly, it is still controversial whether splenectomy should be performed before LT for patients with HIV infection in order to increase the number or function of CD4 cells.

HCV infection control after DDLT is an important factor because the progression of fibrosis is quicker in patients with HIV/HCV coinfection than in patients with HCV infection only (12–14). In 2014, strong direct acting anti-HCV drugs were more commonly available, and currently in Japan, even HIV/HCV coinfected patients are administered DAAs such as sofosbuvir for better outcomes after DDLT (15). Accumulation of results regarding the use of DAAs in Japanese patients, first for HCV mono-infected patients, is necessary.

After implementation of additional points for HIV/HCV coinfected patients for eligibility for DDLT, it became possible to salvage those coinfected patients in whom the prognosis was definitely worse than that for HCV mono-infected patients, especially for those with platelet counts less than 10,000 cells/μl (5). In addition, because those patients were infected with HCV in their childhood, they developed cirrhosis in their 30s or 40s, sometimes with hepatocellular carcinoma. Although only a few patients with HIV/HCV coinfection should be indicated for DDLT, this first report offers special information for such cases.

In conclusion, this is the first report of DDLT performed for an HIV/HCV coinfected hemophilic patient. Meticulous management of ART and clotting factors could lead to the success of DDLT in such cases. Post-transplant anti-HCV therapy will be a key factor to preventing hepatitis recurrence and the progression of fibrosis.

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Conflict of interest None to declare.

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Brief communication

CD4 T lymphocyte counts in patients undergoing splenectomy during living donor liver transplantation☆

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ABSTRACT

The role of splenectomy in increasing the CD4-positive T lymphocyte counts (hereafter: CD4 counts) and the CD4 to CD8 ratio have not yet been fully investigated, especially in the case of HIV-positive patients undergoing liver transplantation (LT).

Methods: The change in the total lymphocyte counts of 32 patients who underwent one-stage splenectomy with living donor (LD) LT with (n = 13) or without rituximab (RTX, n = 19) therapy were examined to validate our cohort of ABO-incompatible LDLT with RTX. Subsequently, perioperative changes in CD4 counts and the CD 4 to CD8 ratio were measured in 13 patients who underwent ABO-incompatible LDLT/RTX with splenectomy.

Results: (1) The administration of RTX did not significantly affect the total lymphocyte counts of patients after LDLT/splenectomy in any of the observation periods. (2) The CD4 counts were significantly higher at 2 years after LDLT in comparison to the perioperative CD4 counts but not within the 3-month period ($p = 0.039$). The CD4/CD8 ratio gradually decreased after LDLT/splenectomy under RTX treatment.

Conclusions: An immediate increase in the CD4 counts therefore cannot be expected after LDLT with splenectomy. The total lymphocyte and CD4 counts were rather stable in the peritransplant period even in ABO incompatible LDLT with RTX.

1. Introduction

In general, liver transplantation (LT) is indicated in HIV-positive end-stage liver failure patients with CD4-positive T lymphocyte counts (hereafter: CD4 counts) of at least 200 or 100/μL in order to prevent opportunistic infection [1,2]. However, patients with hepatic cirrhosis whose HIV is well controlled are sometimes not indicated for liver transplantation if they have a CD4 count that is below baseline due to pancytopenia, which decreases total lymphocyte counts due to portal hypertension. If combined splenectomy improves CD4 counts, subsequent liver transplantation may enable those patients to survive [3]. However, no report is available whether splenectomy can increase CD4 counts when performed during living donor (LD) LT.

In order to clarify the answer to the clinical question, our cohort of ABO incompatible LDLT was assessed and validated, because we measured the CD4 counts only in this cohort to evaluate changes in the T cell and B cell percentages. In fact, in Asian countries, ABO-incompatible LDLT is performed for patients with end-stage liver cirrhosis with the aid of rituximab (RTX) [4,6]. After RTX treatment 1–2 weeks before LT, B cells (CD19/20) are eliminated to almost zero percent. However, there are few reports in the literature regarding the changes of the total lymphocyte counts and CD4 counts in patients who receive RTX treatment before LDLT. If RTX does not affect the CD4 count, our cohort of ABO incompatible LDLT could be valid to investigate the changes in the CD4 counts combined with splenectomy.

2. Objective

We investigated the role of splenectomy in increasing CD4 counts and the CD4 to CD8 ratio performed during LDLT. Analysis 1 was performed to validate our cohort of ABO-incompatible LDLT with RTX. In analysis 2, the changes in the CD4 counts in patients who received RTX treatment before LDLT were clarified.

Abbreviations: CD4, CD4-positive T lymphocyte; LDLT, living donor liver transplantation; LT, liver transplantation; RTX, rituximab.

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3. Patients and methods

3.1. Subjects

Analysis 1: Thirty-two patients who underwent LDLT for various diseases combined with splenectomy in Nagasaki University Hospital between November 2006 and June 2013, and who were observed for at least 1 year, were included. Splenectomy was indicated for thrombocytopenia less than 50,000/μL and hepatitis C liver cirrhosis. Of those 32 patients, 13 patients received RTX 1 week before ABO incompatible LDLT while 19 did not because of ABO matching.

Analysis 2: The above-mentioned 13 patients who underwent ABO incompatible LDLT combined with splenectomy were included in the analysis. All patients received RTX therapy before LDLT. Our method of LDLT was previously reported elsewhere [5].

3.2. Analysis

Analysis 1: The total lymphocyte counts were measured before and after LDLT at various time points until 5 years after LDLT.

Analysis 2: To specifically clarify the effect of splenectomy on CD4 T cell counts and CD4/CD8 ratio, 13 patients were analyzed. The net CD4 counts and the CD4 to CD8 T cell ratio were analyzed at various time points.

3.3. Statistics

All of the data are expressed as the mean and standard deviation or as median values with ranges. The statistical analyses were performed using the Mann–Whitney U test for continuous values and the chi-square test for categorical values. A p-value of <0.05 was considered to be statistically significant. The GraphPad PRISM version 5.0 software program (GraphPad Software, San Diego, CA) was used for all of the statistical analyses.

The study was conducted in accordance with the Declaration of Helsinki of 2013.

4. Results

As shown in Fig. 1, the total lymphocyte counts after LDLT combined with splenectomy did not differ significantly between the patients who received RTX and those who did not in any of the observation periods.

The median CD4 counts (/μL) of the LDLT recipients who underwent splenectomy before the administration of RTX and at 1 month, 3 months, 1 year, and 2 years after treatment were 298, 287, 247, 359, and 441, respectively (Fig. 2). The CD4 counts increased slowly after LDLT, and were significant higher at 2 years and after in comparison to the perioperative count ($p = 0.039$). Furthermore, there was no significant difference in the CD4 counts regardless of splenectomy (Fig. 3).

In addition, the administration of RTX did not influence the CD4/8 ratio after LDLT and splenectomy (Fig. 4). It signifies that CD8 was more enhanced than CD4.

5. Discussion

In the present study we demonstrated that the administration of RTX did not affect the total lymphocyte counts after LDLT combined with splenectomy. Therefore, using the cohort of ABO incompatible LDLT, we found that splenectomy in order to increase the CD4 count before and after LDLT had no therapeutic effect. The present study revealed that in ABO incompatible LDLT with RTX, the total lymphocyte and CD4 counts were rather stable in the peritransplant period and an immediate rise of CD4 count cannot be expected after LDLT with splenectomy.

According to Nomura et al., there is a decrease in the number of CD4 cells in the peripheral blood of patients with liver cirrhosis after splenectomy, which leads to a significant decrease in the CD4/CD8 ratio [7]. As a consequence, splenectomy may not significantly increase the CD4 count before LT. However, Hashimoto et al. reported that the function of CD4 cells in the production of interferon-gamma and CD4 proliferation were increased after splenectomy [8]. Accordingly, it remains controversial whether or not splenectomy should be performed

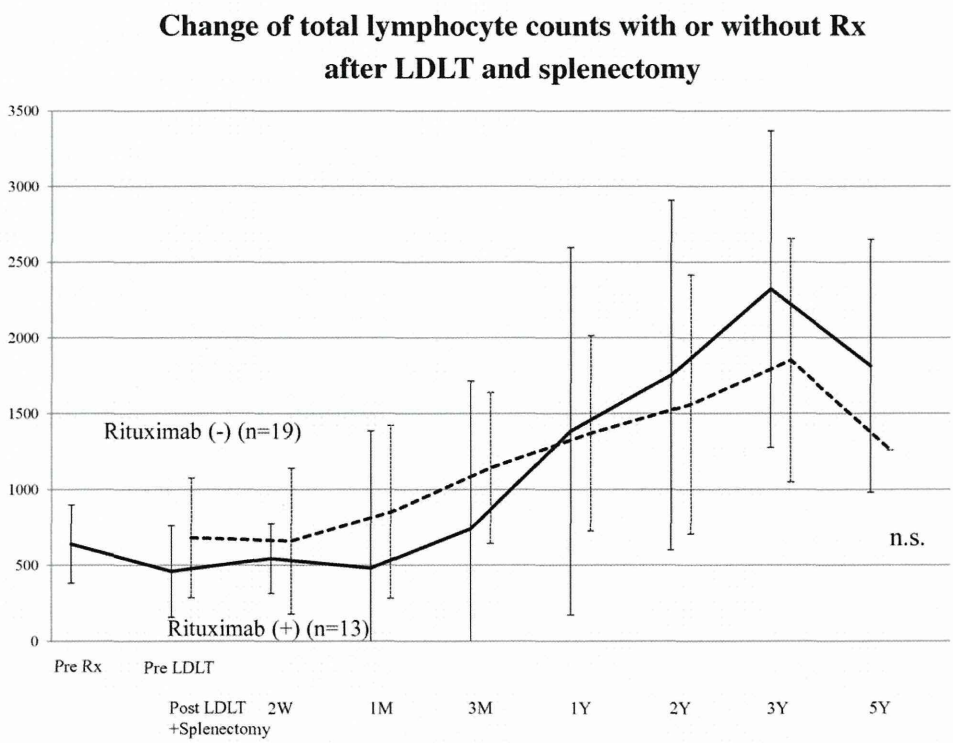

Fig. 1. Change of total lymphocyte counts after LDLT and splenectomy according to the rituximab administration.

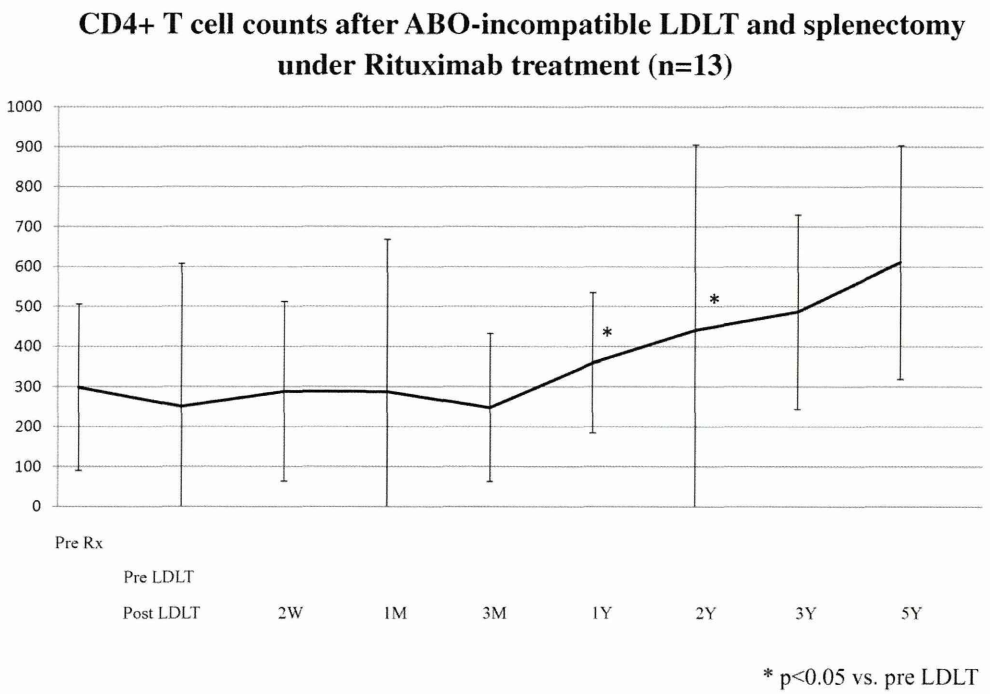

Fig. 2. Changes of CD4 + T cell counts after ABO-incompatible LDLT and splenectomy under rituximab treatment,

before LT in order to increase the number of CD4 cells or the function of the CD4 cells, especially in patients with HIV [9].

In the present study, there was a gradual, long-term increase in the CD4 counts of patients who underwent splenectomy at the time of LT. The short-term decrease in the CD4 count was probably due to surgical stress and the effects of other drugs (e.g., mycophenolate mofetil and interferon). Although our investigation showed that splenectomy did not affect the CD4 count, this may be due to the small number of patients under the specific conditions of the present study (including RTX administration), and should be the subject of a prospective analysis in the future.

Our indication for LT for HIV infected patients was a CD4 count of above 100, since hypersplenism existed due to severe portal hypertension [9]. Immediately after the diseased donor (DD) LT, although the CD4 count dropped below 100, it recovered spontaneously, probably with the aid of splenectomy, which had been planned before DDLT [10]. We believe that if the HIV titer is controlled by antiretroviral therapy, the absolute CD4 count for the indication of LT could be

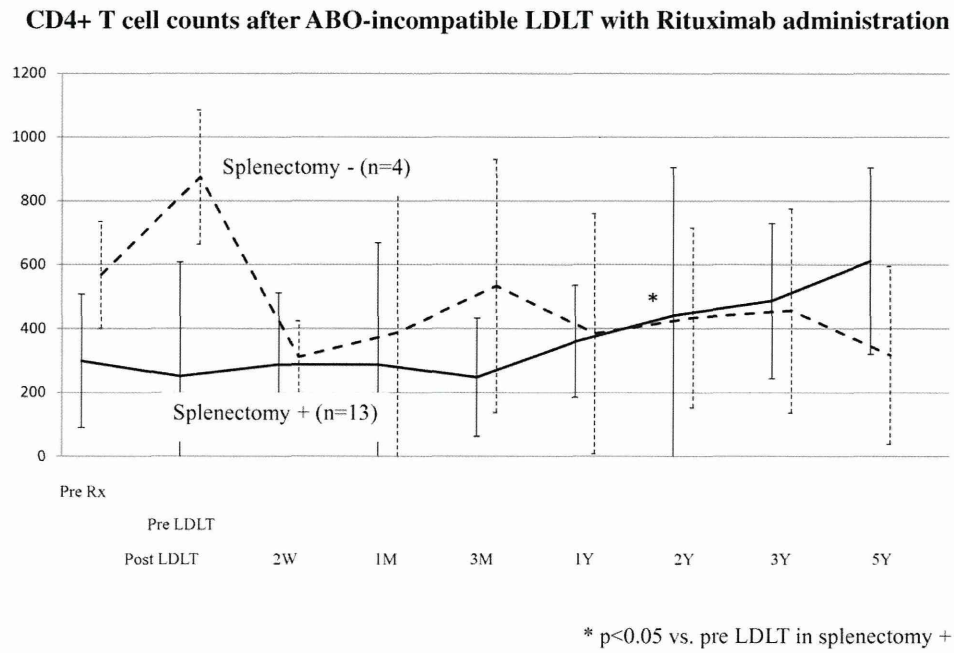

Fig. 3. CD4 + T cell counts after ABO-incompatible LDLT with rituximab administration with or without splenectomy.

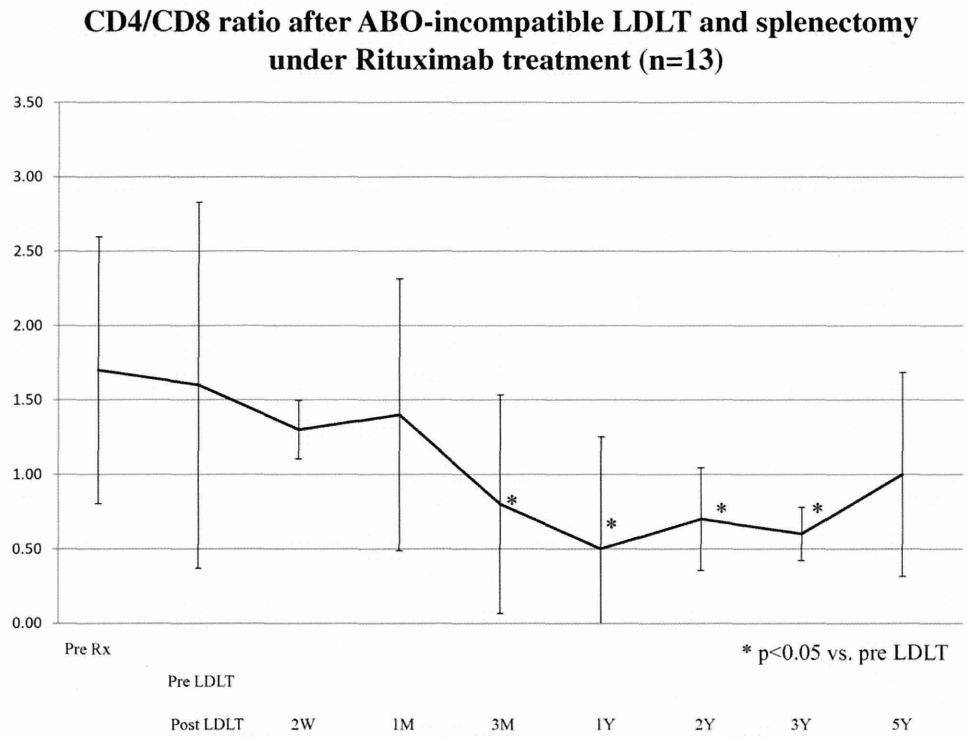

Fig. 4. Changes of CD4/CD8 ratio after ABO-incompatible LDLT and splenectomy under rituximab treatment.

lowered to 100 not 200, since hypersplenism can mask the real immunological function of patients with HIV/HCV coinfection. Furthermore, splenectomy may increase the CD4 count and strengthen the immune function before or during LT. Our results indicate that because the number of CD19/20 B lymphocytes decreased to almost zero after the administration of RTX, the CD8 count should be expected to increase in the early period after LDLT/splenectomy [11]. Since CD4 and CD8 T cells cooperate together, we need to await further investigation on the rate of infection or tumor recurrence after LDLT with RTX and splenectomy in larger studies [12,13].

In conclusion, this is the first report of the effect of splenectomy on the number of CD4 T cells after LDLT. An immediate increase in the CD4 counts therefore cannot be expected after LDLT with splenectomy. The total lymphocyte and CD4 counts were rather stable in the peritransplant period even in ABO incompatible LDLT with RTX.

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