The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Review

J Atheroscler Thromb, 2019; 26: 121-127. http://doi.org/10.5551/jat.RV17029

Liver Transplantation for Homozygous Familial Hypercholesterolemia

Yasushi Ishigaki[1], Naoki Kawagishi[2], Yutaka Hasegawa[1], Shojiro Sawada[3], Hideki Katagiri[3], Susumu Satomi[4] and Shinichi Oikawa[5]

[1]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan
[2]Division of Transplantation Surgery, JCHO Sendai Hospital, Sendai, Japan
[3]Department of Metabolism and Diabetes, Tohoku University Graduate School of Medicine, Sendai, Japan
[4]The Division of Advanced Surgical Science and Technology, Graduate School of Medicine, Tohoku University, Sendai, Japan
[5]Diabetes and Lifestyle-related Disease Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan

Pharmacological treatments to decrease low-density lipoprotein (LDL) cholesterol (LDL-C) have limited effects on patients with homozygous familial hypercholesterolemia (HoFH). Since LDL receptors are located mainly in the liver, liver transplantation is considered to be the only way to correct the hepatic cholesterol metabolism abnormalities in HoFH. Liver transplantations, including those combined with heart transplantation, for HoFH have been increasing since 1984, making this a globally established therapeutic option for HoFH. Plasma LDL-C is reported to be dramatically lowered, by 80%, after transplantation, with the rapid regression of cutaneous and tendinous xanthomas. However, long-term cardiovascular benefits remain unclear. The major concerns about liver transplantation include surgical complications, the need for lifelong immunosuppressive therapy, and rejection. In addition, organ transplantations from deceased donors are extremely rare in Japan. We experienced two pediatric siblings with HoFH who received living-donor liver transplantations from their heterozygous parents. Their plasma LDL-C levels decreased immediately and stabilized at approximately 200 mg/dL. Both developed normally with the administration of lipid-lowering medications and have been free of severe problems for more than 10 years, to date, since transplantation. In Japan, where the shortage of deceased donors is critical, the combination of living-donor liver transplant from a heterozygous donor, that is, usually a parent, and medication is regarded as a valid therapeutic option for HoFH. Further studies and clinical experience are required to establish liver transplantation as a safe and effective treatment for HoFH.

Key words: **Familial hypercholesterolemia, Liver transplantation, Cholesterol metabolism**

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder of cholesterol metabolism, resulting in elevated serum low-density lipoprotein (LDL) cholesterol (LDL-C) and a high incidence of coronary heart disease[1-3]. With the use of statins over the last few decades, the management of LDL-C in FH heterozygotes has improved markedly. On the other hand, pharmacological treatment has a limited effect on both homozygous and compound heterozygous FH cases. In recent years, Lomitapide, which reduces the serum level of LDL-C by inhibiting the function of the microsomal triglyceride transport protein, has been an available therapeutic option for homozygous FH (HoFH) in Japan[4, 5]. However, it has several adverse effects, such as hepatic steatosis and gastrointestinal disorders. LDL apheresis, which intensively lowers both the LDL-C level and the incidence of cardiovascular events, has been established as a standard treatment for HoFH in Japan[3]. However, LDL apheresis is known to be associated with several difficulties, including high cost, long-term maintenance of blood access, and poor quality of life in small infants[6]. In addition, the treatment must be repeated every one to two weeks.

The main pathogenic causes of FH are gene mutations affecting the LDL receptor or the pathways related

Address for correspondence: Yasushi Ishigaki, Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan E-mail: ishigaki@iwate-med.ac.jp

Received: September 30, 2018 Accepted for publication: November 7, 2018

to LDL receptor metabolism. Since an estimated 75% of LDL receptors are located in the liver[7], liver transplantation achieves the replacement of dysfunctional hepatic LDL receptors in patients with HoFH, resulting in near-normal lipoprotein metabolism. Although advanced approaches aimed at achieving adequate LDL metabolism, such as gene therapy or cell transplantation, have also been research goals aiming to treat HoFH, liver transplantation is currently regarded as the only way to correct hepatic abnormal cholesterol metabolism in FH.

Positioning of Liver Transplantation for HoFH Treatment

The first patient undergoing liver transplantation for HoFH was reported by Starzl in 1984[8]. The patient suffered repeated severe attacks of angina, requiring coronary artery bypass graft surgery. At age 6 years, she received combined heart and liver transplantation, resulting in her serum total cholesterol level decreasing from 1,225 to 300 mg/dL, or even lower. Unfortunately, the patient died 3 years after transplantation.

We identified 44 patients who underwent liver transplantation for HoFH in the literature since 1985, as shown in **Table 1**. Ten of these patients had received combined liver and cardiac transplantation, because some had already developed severe coronary artery disease due to hypercholesterolemia[9]. Case reports describing transplantation are now rarely accepted for publication by international peer-reviewed journals. Thus, the current number of liver transplantation cases for HoFH is unclear. In 2015, a retrospective study involving 36 patients with FH undergoing liver transplantation from 2008 to 2014 was reported from Iran[10]. In that study, though several transplant cases were collected, 20% of recipients were FH heterozygotes. The patient characteristics in the Iranian study suggested that the indications for liver transplantation for FH are still controversial. More recently, 8 patients undergoing liver transplantation for HoFH were reported from Turkey[11]. These reports suggest that liver transplantation has become globally established as a therapeutic option for HoFH.

Worldwide, organs for medical transplantation are obtained from deceased donors. As shown in **Table 1**, livers can be transplanted from deceased donors in most HoFH cases. In contrast, a total of 7,474 liver transplantations, mainly for patients with cholestatic diseases, hepatocellular disease and acute liver failure, were carried out in Japan during the period up to 2013. This total included 7,255 living-donor and 219 deceased-donor transplantations, meaning that 97% of transplanted livers were donated by living subjects, while cadaveric liver transplantation was infrequent[12]. This bias in organ donation is a significant issue in the field of medical transplantation in Japan.

Effects of Liver Transplantation for HoFH

The plasma LDL-C levels were dramatically lowered, by 80%, post transplantation in patients with HoFH. At best, the lipid profile would be expected to improve beyond the LDL-C level of the donor, because the deficits of extrahepatic LDL receptors in recipients persist. The marked LDL-C reduction induced the rapid regression of cutaneous and tendinous xanthomas. Although long-term cardiovascular benefits are still unclear, coronary artery stenosis, as evaluated by angiography or intravascular ultrasound, has shown gradual improvement in parallel with LDL-C reductions in many cases[13]. On the other hand, several cases required coronary reperfusion procedures and there were a few mortalities due to progressive coronary artery disease after transplantation[14]. In addition, aortic valve stenosis may develop, despite liver transplantation with normalization of lipid profiles and no history of graft rejection[15]. The clinical course of the cases reported previously suggested that, even with a dramatic LDL-C reduction in response to liver transplantation, it may not be possible to slow the rates of aortic valve disease progression in HoFH once vascular disease has been established. Taken together, these observations indicate that taking the opportunity for liver transplantation is critical for patients with HoFH. The aggressive early lowering of LDL-C by liver transplantation, aimed at preventing the development of severe atherosclerosis and aortic valve stenosis, should be considered before irreversible vascular disease has occurred.

Critical Issues in Liver Transplantation for HoFH

Although liver transplantation for HoFH is presently viewed as the most effective strategy in preventing cardiovascular complications and achieving a definitive cure of this disease, critical concerns remain to be addressed. First, liver transplantation is a very high-risk procedure, necessitating extensive invasion and involving severe potential complications, although its outcomes are generally favorable. The 10-year survival rate exceeds 70% in Japan. Liver transplantation for HoFH cannot be viewed in the same way as that for other fatal diseases, which have no treatment options other than transplantation.

Second, long-term immunosuppressant therapy carries risks of numerous adverse effects. For instance, glucocorticoid administration may induce glucose intol-

Table 1. Reported Cases of Liver Transplantation for Familial Hypercholesterolemia

Age of recipient	Status of donor	Combined transplantation	Complications	Survival time at report	Year	Reference
6	DD	heart		10 weeks	1984	8
17	DD	heart	LF, HF	death after transplantation	1985	19
12	DD	heart	LF, HF	6 months	1986	20
6	DD	heart	hypertension	2 years	1987	21
12	DD			6 months	1988	22
6	DD	heart		5 years	1990	23
17	DD	heart		1 month	1990	23
33	DD	heart	HF		1992	24
4	DD			1 year	1993	25
33	DD	heart		3.7 years	1995	26
9	DD	heart		9 years	1995	27
15	DD			3.8 years	1995	28
10	DD		LF	1 year	1995	28
11	DD				1995	28
18	DD			13 months	2000	29
16	DD			7 months	2000	29
39	DD	heart	HF	3 years	2000	9
46	DD	heart	LF	4 years	2001	30
2	LD			3 years	2003	16
25	DD domino			7 years	2003 2008	31
3	DD			17 months	2004	32
4	LD			1 year	2005	33
16	DD			9 years	2007	34
2	LD		biliary obstruction	2 years	2007	17
17	DD domino			1 year	2009	35
15	DD			1 month	2009	36
11	LD			1 month	2009	36
13	LD			3 months	2011	37
14	LD			3 months	2011	37
9	LD			3 months	2011	37
7	DD			14 months	2011	38
7	DD		LF	3 years	2011	38
11	DD			6 months	2011	14
14	DD			10 years	2011	39
27	DD			3 months	2014	40
7	DD			3 years	2016	15
3	DD			6 years	2016	13
8	DD			5 years	2016	13
17	DD			6 years	2016	13
15	DD			4 years	2016	13
11	DD			1 year	2016	13
3	DD			1 year	2016	13
4	DD			1 year	2016	13
2	DD			1 year	2016	13

DD; deceased donor, LD; living donor, LF; liver failure, HF; heart failure

erance, osteoporosis, and psychosomatic disorders. Tacrolimus, cyclosporine, and mycophenolate mofetil, which are widely used immunosuppressant agents at present, can cause renal damage, heart failure, and myelosuppression. Moreover, insufficient immunosuppression may lead to rejection, which is one of the most serious complications encountered in medical transplantation. Finally, a critical problem in Japan is the lack of organs from deceased donors. At the same time, candidate living donors, usually close relatives of the patient, are restricted in the case of living-donor transplantation.

Sibling Cases of Living-Donor Liver Transplantation for HoFH

We experienced two pediatric siblings with HoFH who received living-donor liver transplantations from their parents who were heterozygous for FH. The elder sibling, a boy, was the subject of the first case report of living-donor liver transplantation for FH worldwide[16]. Both patients developed normally with the administration of lipid-lowering medications and have remained free of severe problems for more than 10 years, to date, since undergoing transplantation.

The elder sibling had presented with an LDL-C level of 898 mg/dL and orange cutaneous xanthomas on the ankles and wrists bilaterally, leading to a diagnosis of HoFH at the age of 1 year. It took several years for him to become accustomed to LDL apheresis, and therapeutic liver transplantation was thus considered. Since the likelihood of receiving a transplant from a deceased donor is very low in Japan, we searched for a normolipidemic subject who might serve as a living donor for liver transplantation, but no suitable candidates were identified. His father's LDL-C level was approximately 170 mg/dL with the administration of simvastatin 10 mg, and that of his mother was approximately 200 mg/dL without medication, suggesting that both his parents were undiagnosed FH heterozygotes. The patient underwent living-donor liver transplantation at age 2 years and 5 months, with his father serving as the donor. His LDL-C concentration immediately dropped below 100 mg/dL postoperatively, and then rose gradually to approximately 200 mg/dL. The administration of pravastatin resulted in an LDL-C decrease to the range expected based on the LDL-C level of the donor. **Fig. 1A** shows the long-term LDL-C level course and the medications used after transplantation. The pravastatin dose was increased gradually, up to 20 mg orally per day. In addition, low-dose ezetimibe was administered, starting 9 years after liver transplantation, and was also increased gradually up to 10 mg daily. As shown in **Fig. 1**, his lipid profile remained well controlled for over 15 years. Moreover, the orange cutaneous xanthomas regressed slowly, and had disappeared 6 years after transplantation. No abnormalities were detected by occasional ultrasound examinations of the carotid artery and heart. Overall, he was growing and developing appropriately for his age, with no episodes of rejection or liver dysfunction.

Two years after the first patient underwent transplantation, his younger sister was born[17]. Her LDL-C was 776 mg/dL just after birth, similar to that of her brother. As the progress of her brother had been good after transplantation, liver transplantation was also considered as a therapeutic strategy for the baby. She was initially listed on the brain-dead donor series of Japan, and waited for 1 year, but no suitable donors became available. She underwent ABO-incompatible living-donor liver transplantation, at age 2 years, with her mother serving as the donor. Her LDL-C concentration decreased immediately after the operation. Pravastatin, as in her brother's case, was administered. Soon after transplantation, the younger sister suffered drug-induced liver dysfunction, though not rejection, as demonstrated by a liver biopsy. Subsequently, 7 months after surgery, she developed common bile duct obstruction, but recovered with stent placement. As shown in **Fig. 1B**, the pravastatin dose was increased gradually to 20 mg per day, and the LDL-C concentration stabilized subsequently within the range of 130−170 mg/dL in response to combined statin and ezetimibe therapy. Despite health problems associated with liver transplantation, such as liver dysfunction and biliary congestion, she developed appropriately for her age.

Both donors have been doing well, without major problems, for more than 10 years, to date, since hepatic transplantation. Both have continued to take lipid-lowering medications, resulting in reasonably good LDL-C concentrations given their heterozygous FH status.

Gene mutation analysis of the LDL receptor gene revealed that the father had a gene mutation at intron 12 (c.1845+2T>C) and the mother had a mutation at exon 15 (c.2193dupC). Thus, these siblings, who underwent liver transplantations from their parents, have compound heterozygous mutations of the LDL receptor gene.

Parents of homozygous FH patients are nearly always heterozygous for FH, and thus benefit from statin therapy. Given that, in Japan, the shortage of deceased donors is critical, a therapeutic strategy combining liver transplantation from a donor heterozygous for FH with cholesterol-lowering drugs is thought to be a promising option for patients who are homozygous or compound heterozygous for FH.

Figure 1 A

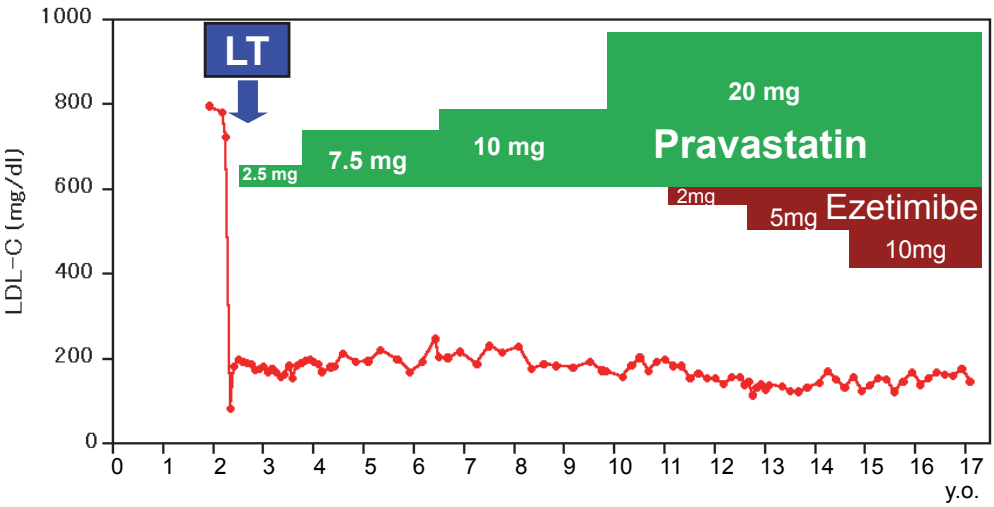

Figure 1 B

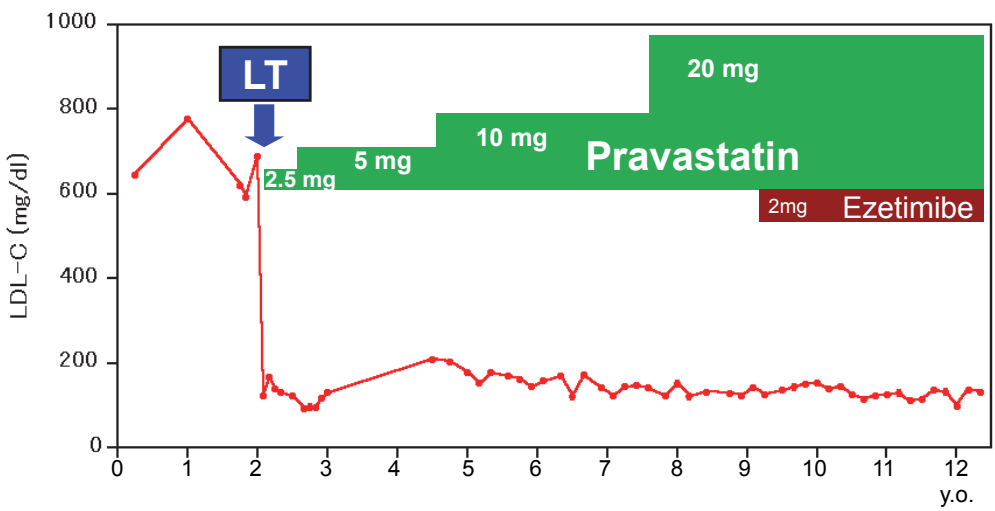

Fig. 1. Time course of lipid profiles and lipid-lowering medication.
(A) Elder sibling, male; (B) younger sibling, female.
Line plot showing plasma LDL-C levels.
LT; liver transplantation.

Conclusion

The consensus panel on HoFH of the European Atherosclerosis Society noted that liver transplantation corrects the molecular defects of LDL clearance, resulting in a marked improvement in LDL-C levels; however, there are obvious disadvantages, including surgical complications and the necessity for lifelong immunosuppressive therapy[18]. Therefore, they positioned liver transplantation as a limited management option applicable only to selected patients.

Based on both the fundamental therapeutic effects and the critical problems of liver transplantation for HoFH, treatment decisions in these cases require careful deliberation. Especially, further studies and clinical experience are needed to establish living-donor liver transplantation, from heterozygous FH donors to HoFH recipients, as a safe and effective therapeutic option.

Conflicts of Interest Statement

The authors reported the following disclosures:

Yasushi Ishigaki has received honoraria from Astellas Pharmaceutical Co., Novartis Pharma K.K., Tanabe-Mitsubishi Pharma Co., Ltd., MSD Co., Ltd., Takeda Pharmaceutical Co., and clinical research funding from Ono Pharmaceutical Co., Ltd.; Hideki Katagiri has received honoraria from Astellas Pharmaceutical Co., Daiichi Sankyo Co. Ltd., Taisho Toyama Pharmaceutical Co., Nippon Boehringer Ingelheim Co. Ltd., and clinical research funding from Ono Pharmaceutical Co., Ltd., Novo Nordisk., Astellas Pharmaceutical Co., Daiichi Sankyo Co. Ltd., Tanabe-Mitsubishi Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., and Sanofi K.K.

Acknowledgments

We greatly appreciate the generous assistance provided by Hiroshi Mabuchi, Atsushi Nohara, and Hayato Tada from Kanazawa University in performing the genetic analyses.

This work was supported by Research on rare and intractable disease, Health, Labour and Welfare Sciences Research Grants.

References

1) Mabuchi H: Half a Century Tales of Familial Hypercholesterolemia (FH) in Japan. J Atheroscler Thromb, 2017; 24: 189-207
2) Harada-Shiba M, Arai H, Ishigaki Y, Ishibashi S, Okamura T, Ogura M, Dobashi K, Nohara A, Bujo H, Miyauchi K, Yamashita S and Yokote K: Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017. J Atheroscler Thromb, 2018; 25: 751-770
3) Harada-Shiba M, Ohta T, Ohtake A, Ogura M, Dobashi K, Nohara A, Yamashita S and Yokote K: Guidance for Pediatric Familial Hypercholesterolemia 2017. J Atheroscler Thromb, 2018; 25: 539-553
4) Harada-Shiba M, Ikewaki K, Nohara A, Otsubo Y, Yanagi K, Yoshida M, Chang Q and Foulds P: Efficacy and Safety of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolemia. J Atheroscler Thromb, 2017; 24: 402-411
5) Nohara A, Otsubo Y, Yanagi K, Yoshida M, Ikewaki K, Harada-Shiba M and Jurecka A: Safety and Efficacy of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolemia (HoFH): Results from the AEGR-733-301 Long-Term Extension Study. J Atheroscler Thromb, 2018;
6) Makino H, Tamanaha T and Harada-Shiba M: LDL apheresis in Japan. Transfus Apher Sci, 2017; 56: 677-681
7) Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS: Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. N Engl J Med, 1984; 311: 1658-1664
8) Starzl TE, Bilheimer DW, Bahnson HT, Shaw BW, Jr., Hardesty RL, Griffith BP, Iwatsuki S, Zitelli BJ, Gartner JC, Jr., Malatack JJ, Urbach AH: Heart-liver transplantation in a patient with familial hypercholesterolaemia. Lancet, 1984; 1: 1382-1383
9) Alkofer BJ, Chiche L, Khayat A, Deshayes JP, Lepage A, Saloux E and Reznik Y: Liver transplant combined with heart transplant in severe heterozygous hypercholesterolemia: report of the first case and review of the literature. Transplant Proc, 2005; 37: 2250-2252
10) Mansoorian M, Kazemi K, Nikeghbalian S, Shamsaeefar A, Mokhtari M, Dehghani SM, Bahador A, Salahi H, Amoozgar H and Malek Hosseini SA: Liver transplantation as a definitive treatment for familial hypercholesterolemia: A series of 36 cases. Pediatr Transplant, 2015; 19: 605-611
11) Alim A, Tokat Y, Erdogan Y, Gokkaya Z, Dayangac M, Yuzer Y and Oezcelik A: Liver transplantation for homozygote familial hypercholesterolemia: the only curative treatment. Pediatr Transplant, 2016; 20: 1060-1064
12) Umeshita K, Inomata Y, Furukawa H, Kasahara M, Kawasaki S, Kobayashi E, Kokudo N, Sakisaka S, Shimada M, Tanaka E and Uemoto S: Liver transplantation in Japan: Registry by the Japanese Liver Transplantation Society. Hepatol Res, 2016; 46: 1171-1186
13) Martinez M, Brodlie S, Griesemer A, Kato T, Harren P, Gordon B, Parker T, Levine D, Tyberg T, Starc T, Cho I, Min J, Elmore K, Lobritto S and Hudgins LC: Effects of Liver Transplantation on Lipids and Cardiovascular Disease in Children With Homozygous Familial Hypercholesterolemia. Am J Cardiol, 2016; 118: 504-510
14) El-Rassi I, Chehab G, Saliba Z, Alawe A and Jebara V: Fatal cardiac atherosclerosis in a child 10 years after liver transplantation: a case report and a review. J Clin Lipidol, 2011; 5: 329-332
15) Greco M, Robinson JD, Eltayeb O and Benuck I: Progressive Aortic Stenosis in Homozygous Familial Hypercholesterolemia After Liver Transplant. Pediatrics, 2016; 138:
16) Shirahata Y, Ohkohchi N, Kawagishi N, Syouji M, Tsukamoto S, Sekiguchi S, Koyamada N, Oikawa S and Satomi S: Living-donor liver transplantation for homozygous familial hypercholesterolemia from a donor with heterozygous hypercholesterolemia. Transpl Int, 2003; 16: 276-279
17) Kawagishi N, Satoh K, Akamatsu Y, Sekiguchi S, Ishigaki Y, Oikawa S and Satomi S: Long-term outcome after living donor liver transplantation for two cases of homozygous familial hypercholesterolemia from a heterozygous donor. J Atheroscler Thromb, 2007; 14: 94-98
18) Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O and Chapman MJ: Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur

Heart J, 2014; 35: 2146-2157
19) Shaw BW, Jr., Bahnson HT, Hardesty RL, Griffith BP and Starzl TE: Combined transplantation of the heart and liver. Ann Surg, 1985; 202: 667-672
20) Figuera D, Ardaiz J, Martin-Judez V, Pulpon LA, Pradas G, Cuervas-Mons V, Burgos R, Arcas M, Pardo F, Cienfuegos JA: Combined transplantation of heart and liver from two different donors in a patient with familial type IIa hypercholesterolemia. J Heart Transplant, 1986; 5: 327-329
21) Fricker FJ, Griffith BP, Hardesty RL, Trento A, Gold LM, Schmeltz K, Beerman LB, Fischer DR, Mathews RA, Neches WH, Park SC, Zuberbuhler JR, Lenox CC, Bahnson HT: Experience with heart transplantation in children. Pediatrics, 1987; 79: 138-146
22) Valdivielso P, Escolar JL, Cuervas-Mons V, Pulpon LA, Chaparro MA and Gonzalez-Santos P: Lipids and lipoprotein changes after heart and liver transplantation in a patient with homozygous familial hypercholesterolemia. Ann Intern Med, 1988; 108: 204-206
23) Bahnson HT and Gordon RD: Transplantation of other organs with the heart. Cardiovasc Clin, 1990; 20: 237-248
24) Barbir M, Khaghani A, Kehely A, Tan KC, Mitchell A, Thompson GR and Yacoub M: Normal levels of lipoproteins including lipoprotein(a) after liver-heart transplantation in a patient with homozygous familial hypercholesterolaemia. Q J Med, 1992; 85: 807-812
25) Sokal EM, Ulla L, Harvengt C and Otte JB: Liver transplantation for familial hypercholesterolemia before the onset of cardiovascular complications. Transplantation, 1993; 55: 432-433
26) Rela M, Muiesan P, Heaton ND, Corbally M, Hajj H, Mowat AP, Williams R and Tan KC: Orthotopic liver transplantation for hepatic-based metabolic disorders. Transpl Int, 1995; 8: 41-44
27) Tellez de Peralta G and Burgos Lazaro R: [Multiple organ transplants]. Rev Esp Cardiol, 1995; 48 Suppl 7: 46-50
28) Revell SP, Noble-Jamieson G, Johnston P, Rasmussen A, Jamieson N and Barnes ND: Liver transplantation for homozygous familial hypercholesterolaemia. Arch Dis Child, 1995; 73: 456-458
29) Lopez-Santamaria M, Migliazza L, Gamez M, Murcia J, Diaz-Gonzalez M, Camarena C, Hierro L, De la Vega A, Frauca E, Diaz M, Jara P and Tovar J: Liver transplantation in patients with homozygotic familial hypercholesterolemia previously treated by end-to-side portocaval shunt and ileal bypass. J Pediatr Surg, 2000; 35: 630-633
30) Offstad J, Schrumpf E, Geiran O, Soreide O and Simonsen S: Plasma exchange and heart-liver transplantation in a patient with homozygous familial hypercholesterolemia. Clin Transplant, 2001; 15: 432-436
31) Popescu I, Simionescu M, Tulbure D, Sima A, Catana C, Niculescu L, Hancu N, Gheorghe L, Mihaila M, Ciurea S and Vidu V: Homozygous familial hypercholesterolemia: specific indication for domino liver transplantation. Transplantation, 2003; 76: 1345-1350
32) Moyle M and Tate B: Homozygous familial hypercholesterolaemia presenting with cutaneous xanthomas: response to liver transplantation. Australas J Dermatol, 2004; 45: 226-228
33) Khalifeh M, Faraj W, Heaton N, Rela M and Sharara AI: Successful living-related liver transplantation for familial hypercholesterolemia in the Middle East. Transpl Int, 2005; 17: 735-739
34) Schmidt HH, Tietge UJ, Buettner J, Barg-Hock H, Offner G, Schweitzer S, Dedoussis GV, Rodeck B, Kallfelz HC, Schlitt HJ, Oldhafer K and Klempnauer J: Liver transplantation in a subject with familial hypercholesterolemia carrying the homozygous p.W577R LDL-receptor gene mutation. Clin Transplant, 2008; 22: 180-184
35) Liu C, Niu DM, Loong CC, Hsia CY, Tsou MY, Tsai HL and Wei C: Domino liver graft from a patient with homozygous familial hypercholesterolemia. Pediatr Transplant, 2010; 14: E30-33
36) Kakaei F, Nikeghbalian S, Kazemi K, Salahi H, Bahador A, Dehghani SM, Dehghani M, Nejatollahi SM, Shamsaeefar A, Khosravi MB and Malek-Hosseini SA: Liver transplantation for homozygous familial hypercholesterolemia: two case reports. Transplant Proc, 2009; 41: 2939-2941
37) Kucukkartallar T, Yankol Y, Kanmaz T, Topaloglu S, Acarli K and Kalayoglu M: Liver transplantation as a treatment option for three siblings with homozygous familial hypercholesterolemia. Pediatr Transplant, 2011; 15: 281-284
38) Maiorana A, Nobili V, Calandra S, Francalanci P, Bernabei S, El Hachem M, Monti L, Gennari F, Torre G, de Ville de Goyet J and Bartuli A: Preemptive liver transplantation in a child with familial hypercholesterolemia. Pediatr Transplant, 2011; 15: E25-29
39) Palacio CH, Harring TR, Nguyen NT, Goss JA and O'Mahony CA: Homozygous familial hypercholesterolemia: case series and review of the literature. Case Rep Transplant, 2011; 2011: 154908
40) Page MM, Ekinci EI, Jones RM, Angus PW, Gow PJ and O'Brien RC: Liver transplantation for the treatment of homozygous familial hypercholesterolaemia in an era of emerging lipid-lowering therapies. Intern Med J, 2014; 44: 601-604