中文題目: 慢性C型肝炎使用DAA治療後的免疫反應是否與活體肝移植術後膽道併發症和急性排斥有關？

英文題目: Is Immune Response of DAA Therapy on Chronic Hepatitis C Related to post-Living Donor Liver Transplantation Biliary Complication and Acute Cellular Rejection?

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Background & Aims:

Direct-acting antivirals (DAAs) have revolutionized the care of patients with hepatitis C virus (HCV) infection, with cure rate of more than 90%. From the perspectives of living donor liver transplantation (LDLT), suppression of immune response is reported to associate with better graft function. However, alteration of immune response following pre-LDLT DAA therapy in chronic HCV infected patients may lead to post-transplant non-surgical complications, such as immune-mediated biliary complication and acute cellular rejection (ACR). Herein, we would like to explore the association between the changes of immunity and allograft injury (biliary complication and ACR) in chronic hepatitis C recipients with pre-LDLT DAA therapy.

Method:

This cohort observational study enrolled total 153 HCV-infected recipients who underwent LDLT from January 2015 to February 2021 in our liver transplantation program. Pre-LDLT and post-LDLT day-30 (POD 30) of serum anti-HCV antibody titer and incidence of (BC and ACR) after LDLT were recorded. Biliary complication was defined as post-LDLT requiring biliary stenting, episode of post-LDLT biliary tract infection requiring hospitalization and systemic antibiotic treatment or revision of biliary tract anastomosis. ACR was determined based on the histologic report of liver graft biopsy.

Results:

Among 153 LDLT recipients, 31 (20.3%) treated with pre-LDLT DAA therapy (defined as DAA group), and 122 (79.7%) without pre-LDLT DAA treatment (named DAA naïve group) (Table 1). After a mean follow-up of 43.2 months, DAA group had a higher rate of aviremia, in both of the before and after LDLT (3.2% vs. 43.4%, p = 0.0006; 0% vs. 33.6%, p < 0.0001, respectively). Higher incidence of post-LDLT biliary complication was observed in DAA group (32.3% vs. 14.8%, p = 0.028) (Figure 1). Compared to pre-LDLT, elevation of anti-HCV antibody titer after LDLT was observed among all of the recipients (DAA group vs. DAA naïve group: p = 0.0001 vs. p = 0.0006, respectively) (Figure 2A, 2B), and the magnitude of mean anti-HCV titer fluctuation is more significant in the DAA group (p = 0.0024) (Figure 2C). Among the recipients with biliary complication (n=28, 18.3%) and acute cellular rejection (n=41, 26.8%), those in DAA group have significant magnitude of mean anti-HCV Ab titer up-regulation, compared to those without pre-LDLT DAA therapy (34.87 ± 24.41 vs. 16.36 ± 24.08,

p= 0.05; 34.07 ± 27.44 vs. 13.82 ± 11.34, *p* < 0.005, respectively) (Table 2).

Conclusion:

In the setting of LDLT for chronic hepatitis C recipients, our current data found that patients in DAA group had a higher incidence of post-LDLT biliary complication. A more significant magnitude of mean anti-HCV titer up-regulation was observed in the DAA group of LDLT recipients who developed biliary complication and ACR. These clinical observations might be caused by the activation of HCV-specific immune response following viral clearance with pre-LDLT DAA therapy. We postulated that altered immunological response and restoration of immune function after DAA therapy might interfere healing and fibrosis process of biliary anastomosis, consequently, lead to a higher rate of post-LDLT biliary anastomotic stricture. Previous researches regarding both innate and adaptive immunopathological mechanisms, including T cell exhaustion due to chronic HCV infection and T cell reactivation after DAA use, may provide the explanation of these phenomena. Further investigations are required to clarify the exact mechanism, which may shed light on optimizing the pre-LDLT planning, donor selection strategy and wane the incidence and severity of both post-transplant biliary complication and acute cellular rejection in the future.

In conclusion, we speculated that the immune response of pre-LDLT DAA therapy on chronic hepatitis C, which might be reflected in the fluctuation of pre- and post-LDLT mean anti-HCV titer, was associated with the allograft injury, including biliary complication and acute cellular rejection.

Table.1 Baseline characteristics of 153 HCV-infected recipients underwent LDLT

Sex, *n (%)*	Male / Female	72 (47.7) / 81 (52.3)
Follow up (months), mean		43.6
Age of transplant (years), mean		54.5
HCV NAT positive, *n (%)*	Pre-LDLT / Post-LDLT	70 (45.8) / 61 (39.9)
Anti-HCV treatment, *n (%)*	Pre-LDLT DAA	31 (20.3)
	Post-LDLT DAA	48 (31.4)
	DAA naïve	74 (48.4)
HCV genotype, *n (%)*	1/2/3/6/undetected	52 (34.0) / 38 (24.8) / 2 (1.3) / 2 (1.3) / 59 (38.6)
AFP (ng/mL), mean ± SD	Pre transplant	14.1 ± 70.0
	At transplant activation	3.8 ± 7.3
Liver donor, *n (%)*	Living donor / Deceased donor	136 (88.9) / 17 (11.1)
HCC diagnosed at LDLT, *n (%)*	Absent / Present	80 (52.3) / 73 (47.7)
MELD score, mean ± SD		18.0 ± 18.7
Liver explant pathology	Viable tumor identified, *n (%)*	60 (39.2)
	Largest tumor (cm), mean ± SD	2.9 ± 3.0
	Number of lesions, mean	2.5
	Lymphovascular invasion, *n (%)*	16 (10.5)
Bridging therapy, *n (%)*	Any	51 (33.3)
	TACE	31 (20.3)
	Ablative therapy	28 (18.3)
	TARE	1 (0.6)
	Proton	3 (1.96)
	Resection	7 (4.6)
Post-LDLT complications, *n (%)*	Biliary complication*	28 (18.3)
	Acute cellular rejection	41 (26.8)
Post-LDLT de novo HCC / Recurrence, *n (%)*		6 (3.9) / 0

*Biliary complication, defined as post-LDLT requiring biliary stenting, episode of post-LDLT biliary tract infection requiring hospitalization and systemic antibiotic treatment or revision of biliary anastomosis.

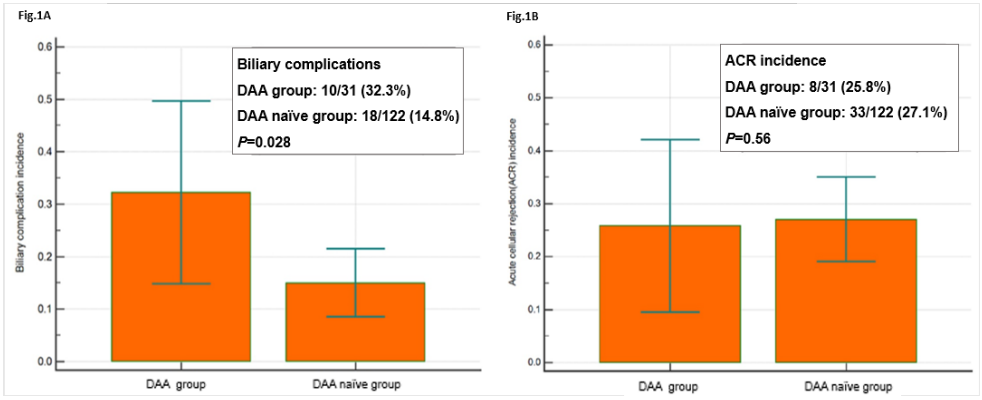

Fig.1: Comparison of incidence of biliary complication (Fig.1A) and acute cellular rejection (Fig.1B) between DAA group and DAA naïve group

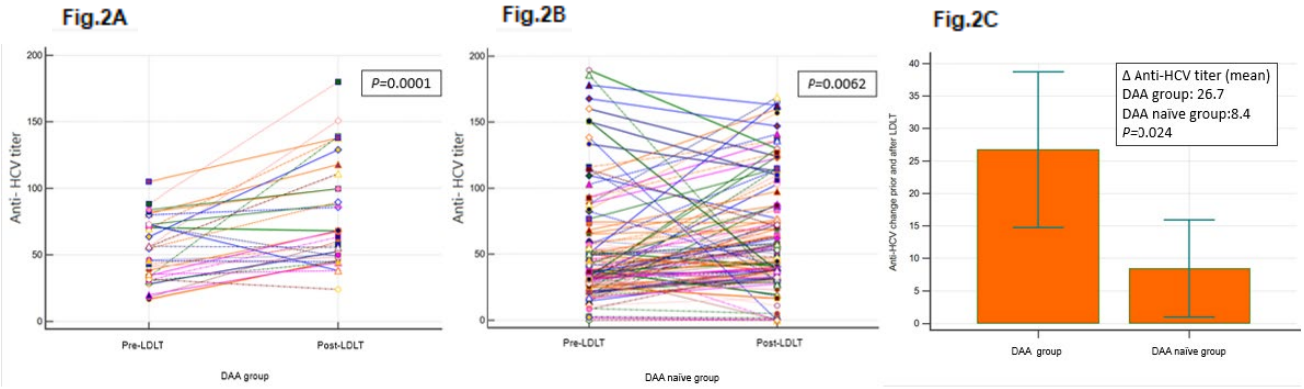

Fig 2A, 2B: Fluctuation of anti-HCV Ab titer before and after LDLT between DAA group and DAA naïve group

Fig 2C: Comparison of Δ anti-HCV titer before and after LDLT between DAA group and DAA naïve group

Table 2. The association between fluctuation of mean anti-HCV Ab titer vs. biliary complication and acute cellular rejection after living donor liver transplantation. (Student's *t* test, tails = 1, type = 2)

Category	Biliary complication N = 28 (18.3%)				Acute cellular rejection N = 41 (26.8%)			
	Up regulation N = 19 (67.9%)		Down regulation N = 9 (32.1%)		Up regulation N = 29 (70.7%)		Down regulation N = 12 (29.3%)	
Anti-HCV Ab titer	25.13 ± 25.39[a]		-20.39 ± 27.08[b]		18.71 ± 18.81[c]		-23.18 ± 23.55[d]	
	DAA (+) N = 9	DAA (-) N = 10	DAA (+) N = 1	DAA (-) N = 8	DAA (+) N = 7	DAA (-) N = 22	DAA (+) N = 1	DAA (-) N = 11
	34.87 ± 24.41[e]	16.36 ± 24.08[f]	-2.55	-22.63 ± 28.05	34.07 ± 27.44[g]	13.82 ± 11.34[h]	-23.14	-23.18 ± 24.71
	p = 0.05				p <0.005			

a vs b: p <0.001; c vs d: p <0.001

a vs c: p >0.05; b vs d: p >0.05

e vs f: p = 0.05; g vs h: p <0.005