

# Impact of Donor-Specific Anti-HLA and Anti-Angiotensin-II Type 1 Receptor Antibodies on Graft Fibrosis after Immunosuppression Withdrawal in Pediatric Liver Transplantation

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Pediatric living-donor liver transplant (LDLT) recipients can often exhibit a reduction or cessation of immunosuppression (IS); over the long term, a high incidence of progressive graft fibrosis is of particular concern. We conducted a cross-sectional study to examine the effects of donor-specific anti-HLA antibody (DSA) and angiotensin II type-1 receptor antibody (anti-AT1R) on post-transplant graft fibrosis. Fifty-eight pediatric LDLT patients who underwent IS withdrawal and had a follow-up biopsy were studied. The patients were classified into two groups according to their pathological status: severe fibrosis (Group-SF) (Ishak score $\geq$ 3) and mild fibrosis (Group-MF) (Ishak score $\leq$ 2). We used LABScreen Single Antigen beads to detect DSA and ELISA to detect anti-AT1R. All patients except one did not develop DSA-Class I. The strength of DSA-DRB1 was significantly higher in Group-SF than in Group-MF (MFI 8889 vs. 477,  $p<0.001$ ), which resulted in a significantly higher percentage of high-level DSA-DRB1 (MFI $>5000$ ) in Group-SF than in Group-MF (50% vs. 3%,  $p<0.001$ ). The frequency of high-level anti-AT1R patients ( $>17.0$  U/ml) was significantly higher in Group-SF than Group-MF (71% vs. 39%,  $p=0.03$ ).

The frequency of high-level DSA and anti-AT1R							
	total	DSA-Class I (MFI $>5000$ )	DSA-Class II (MFI $>5000$ )	DSA-DQB1 (MFI $>5000$ )	DSA-DRB1 (MFI $>5000$ )	DSA-DRB345 (MFI $>5000$ )	Anti-AT1R ( $>17$ U/ml)
Mild fibrosis (Ishak $\leq$ 2)	41	1 (3%)*	18 (47%)*	16 (42%)*	1 (3%)*	6 (16%)*	16 (39%)
Severe fibrosis (Ishak $\geq$ 3)	17	0**	10 (63%)**	6 (38%)**	8 (50%)**	2 (13%)**	12 (71%)
		P=0.51	P=0.31	P=0.75	<b>P&lt;0.001</b>	p=0.82	<b>p=0.03</b>

"\*": HLA-typing was unknown in 3 patients. \*\*": HLA-typing was unknown in 1 patients . "

When patients were categorized according to their DSA-DRB1 and anti-AT1R level, all patients with both high-level DSA-DRB1 and high-level anti-AT1R had developed severe fibrosis.

The predictive value of DSA-DRB1 and anti-AT1R		
DSA-DRB1>5000 / anti-AT1R>17	Mild fibrosis (n=38)	Severe fibrosis (n=16)
- / -	23 (92%)	2 (8%)
- / +	14 (70%)	6 (30%)
+ / -	1 (33%)	2 (67%)
+ / +	0	6 (100%)

P<0.001

We concluded that assessing anti-AT1R along with DSA-DRB1 provide additional information, and both HLA and non-HLA immunity may be involved in graft fibrosis after IS withdrawal.