간부전 환자는 신부전 환자보다 IgG 동종응집소 역가가 높다

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Liver Failure Has Higher IgG ABO Blood Group Isoagglutinin Titer than Kidney Failure

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Background: In ABO-incompatible (ABOi) solid organ transplantation, the minimization and management of isoagglutinin (IA) against donor ABO antigens between before and two weeks after transplantation is important for preventing hyper-acute rejection. Several factors that can affect the IA titer have been reported. This is the first study to evaluate whether there are IA titer differences between kidney transplantation (KT) and liver transplantation (LT) recipients.

Methods: Thirty-eight KT and 32 LT type O recipients, who underwent ABOi KT or LT between March 2013 and March 2018, were enrolled consecutively. The IgM IA and IgG IA titers of the LT and KT recipients at different time points (initial, operation day [day-0], postoperative one week, four weeks, and one year) were evaluated.

Results: The LT recipients showed higher initial IgG IA titers than the KT recipients ($P=0.01$). This higher titer in the LT recipients persisted during the critical phase (from before transplantation to postoperative one week). The IgG and IgM IA titers were similar in the KT and LT recipients at postoperative four weeks.

Conclusion: The difference in IA titer between the underlying diseases should be considered in the desensitization protocol before ABOi SOT. (*Korean J Blood Transfus* 2021;32:112-122)

Key words: Liver transplantation, Kidney transplantation, ABO blood-group system, Desensitization, immunologic, Agglutinins

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Introduction

Kidney transplantation (KT) and liver transplantation (LT) are the most frequently performed solid organ transplantation (SOT). The transplanted organs are donated from brain dead or living people. Owing to the shortage of deceased donors, ABO-incompatible (ABOi) transplantation has been performed to expand the indication for living donor transplantation [1]. According to a recently published annual report by the National Organ Tissue Management Center, the proportion of ABOi transplantation is 26.39% (709/2,687) in living donor transplantation in Korea: 29.35% (440/1,499) in KT and 22.64% (269/1,188) in LT [2].

In ABOi SOT, isoagglutinin (IA) antibodies directed against donor ABO antigens can lead to rejection within minutes to hours (hyperacute rejection) [3]. Therefore, minimization and management of the recipients' anti-donor IA titers between before and two weeks after ABOi transplantation are important for preventing hyperacute rejection and achieving a better prognosis [1,4]. Several population factors, such as age, gender, and race [5], can affect the IA titer. On the other hand, differences in the IA titer according to the underlying disease, such as kidney and liver disease, have not been reported. To the best of the authors' knowledge, this is the first study to evaluate whether IA titer differences exist between ABOi KT and LT recipients.

Materials and Methods

This was a single-center retrospective study ap-

proved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (SMC 2018-08-161). The requirement of informed consent was waived because of its retrospective nature. Because the characteristics of IA vary according to the ABO blood type [6], this study only analyzed the recipients with a single blood type. The target blood type was type O, which accounted for most (40.3%) of the ABOi transplants in 2018. Consecutive type O recipients who underwent ABOi KT or LT at the Samsung Medical Center between March 2013 and March 2018 were enrolled in this study. Their medical records were reviewed retrospectively to obtain data, such as the demographics, ABO types of donors and recipients, and serial IA titers of the recipients.

In ABOi KT and LT recipients, Rituximab (RTX) (Genentech Inc., San Francisco, CA, USA) was administered 14 days before transplantation. Plasmapheresis (PP) was performed every second day for one or two weeks before transplantation and continued until the IgG IA titers reached the target levels [7]. At the authors' institute, the target anti-donor IA titers were 1:16 LT (IA type was unspecified) and 1:32 in KT (IgG IA). Daily PP (1.5 plasma volumes) was performed if the target IgG IA titers were not reached [8]. Transplantation was performed at the clinician's discretion if the IA titer performed on the next day after the daily PP remained the same for three consecutive measurements.

The IA titers were determined using the tube method. The test cells (3% group A1 and B cells) were obtained from Affirmagen (Ortho-Clinical Diagnostics, Raritan, NJ, USA). For both IgM and IgG

assays, the test cells were combined with the patient's serum sample at a ratio of 1:2 and centrifuged at 3400 rpm for 15 sec. For the IgM assay, 500 μ L of the serum samples were first serially diluted with 500 μ L of saline and then incubated with the test cells at room temperature for 15 min. For the IgG assay using anti-human globulin (AHG), the serum samples were preincubated with 0.01M dithiothreitol (DTT) at 37°C for 30 min, serially diluted, and incubated with the test cells at 37°C for 30 min. The last dilution showing 1+ reactivity was defined as the anti-A or anti-B antibody titer value in each assay. The IA titers were checked before administering RTX and were measured daily after starting PP until discharge. The IA titer was followed up daily until postoperative two weeks. The titer was then checked weekly for the first one month. Subsequently, it was checked at two, three, six, and 12 months. The IA titration was performed on both anti-donor and non-anti-donor IA before transplantation (initial and day 0). After transplantation, only anti-donor IA was checked. The IA titer was log2 converted for the evaluation. The IgG and IgM IA titers of the KT and LT recipients at each time point were compared. The total protein-albumin (calculated globulin, CG) level of each group was evaluated to approach the globulin status [9].

The demographic data and basic characteristics of the recipients and donors were evaluated. The differences between the categorical variables were analyzed using a chi-square test. Normality was assessed using the Shapiro-Wilk normality test. A Student's t-test was performed for data with a normal distribution, while the Wilcoxon-Mann-Whitney test was performed for data with a non-normal

distribution. Linear regression analysis was performed, and Pearson's correlation coefficient (r) was calculated to determine the relationship between the CG level and IA. All statistical analyses were performed using Analyse-it v5.10 (Analyse-it Software, Leeds, UK) and IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). P values <0.05 were considered statistically significant.

Results

During the study period, there were 694 cases of KT and 637 cases of LT. The number of living donors was 337 for KT and 381 for LT. The proportion of ABOi cases was 19.9% (75/377) in KT and 24.1% (92/381) in LT. The final enrolled type O recipients accounted for 50.7% (38/75) in ABOi KT and 34.8% (32/92) in ABOi LT (Fig. 1). Two LT recipients were excluded because they were younger than one year old. Seventy recipients who met the inclusion criteria of this study were finally analyzed. Table 1 lists the clinical characteristics of the patients.

When the KT and LT recipients were compared, the IgG IA titer tended to be significantly higher in the LT recipients before transplantation ($P=0.01$). The median IgG IA titers were initially (before transplantation) 8.0 and 9.0 in the KT and LT recipients, respectively. IgM IA was not higher in the LT recipients initially ($P=0.20$). On day-0 and at postoperative one week, the IgG and IgM IA titers were significantly higher in the LT recipients than the KT recipients (Fig. 2). However, the IgG and IgM IA titers were similar in the KT and LT recipients at postoperative four weeks and one year. The

Fig. 1. Flowchart showing the selection of study subjects based on the isoagglutinin titers in KT and LT recipients and the inclusion criteria of this study.

Abbreviations: KT, kidney transplant; LT, liver transplant.

LT recipients showed significantly higher CG levels initially ($P < 0.01$). On the other hand, after RTX administration, there was no significant difference in the CG level between the LT and KT recipients ($P = 0.19$ on day 0, $P = 0.21$ at postoperative one week, and $P = 0.08$ at postoperative four weeks).

Correlation analyses of the IgG and IgM IA titers with CG levels yielded positive Pearson's r values of 0.44 and 0.61, respectively ($P < 0.01$ for both). Fig. 3 shows the results of linear regression analysis for the relationship between the IgG and IgM IA titers and the CG level.

Discussion

Three types of immune response have been observed in ABOi transplantation recipients: rejection,

tolerance, and accommodation [10]. To prevent hyperacute rejection, management of the IA titer from day 0 to postoperative two weeks is critical [11,12] because there will be no more rejection (accommodation) if the first critical phase of approximately two weeks is managed successfully. Desensitization plans, including PP and RTX administration, are based on the IA titers with the goal of achieving an anti-donor IA titer of 16 or less before transplantation. The number of necessary PP before transplant is estimated by the IA titer [13,14]. Higher IA titers in LT recipients may require greater numbers of PP before and within the first two weeks after transplantation. The RTX dosage is also associated with the IA titer. A low dose of RTX is adequate in ABOi transplant recipients with low IA titers [15]. In this study, the IgG IA titer was

Table 1. Clinical characteristics of the recipients

	KT	LT	<i>P</i> value
No. of recipients	38	30	
Recipient age, median (IQR)	42.5 (36.0~55.0)	52.0 (49.0~59.1)	<0.01
Recipient, male (%)	19 (50.0)	23 (76.7)	0.04
Underlying disease	DM nephropathy 10 (26.3) IgA 7 (18.4) GN 3 (7.9) ADPCK 3 (7.9) Other 7 (18.4) Unknown 8 (21.1)	HCV with LC 21 (70.0) LC 7 (23.3) PBC 2 (6.7)	
Initial log2 anti-donor IA IgM titer, median (IQR)	6.0 (5.0~7.0)	6.0 (5.0~8.0)	0.20
Initial log2 anti-donor IA IgG titer, median (IQR)	8.0 (6.0~10.0)	9.0 (8.0~10.0)	0.01
Initial calculated globulin (mg/dL), median (IQR)	2.6 (2.3~2.9)	2.8 (2.5~3.2)	0.04
Plasmapheresis	38 (100.0)	30 (100.0)	
Induction therapy			
ATG+RTX	36 (94.7)	0 (0.0)	
RTX+Basiliximab	0 (0.0)	14 (46.7)	
RTX	0 (0.0)	16 (53.3)	
ATG	2 (5.3)	0 (0.0)	
Maintenance			
FK+MMF+PD	38 (100.0)	30 (100.0)	
Donor ABO type			
A (%)	19 (50.0)	15 (50.0)	0.90
B (%)	16 (42.1)	12 (40.0)	
AB (%)	3 (7.9)	3 (10.0)	

Abbreviations: KT, kidney transplant; LT, liver transplant; IQR, interquartile range; ATG, anti-thymocyte globulin; RTX, rituximab; FK, FK506; MMF, mycophenolate mofetil; PD, prednisolone; DM, diabetes mellitus; IgA, IgA nephropathy; GN, glomerulonephritis; ADPCK, autosomal dominant polycystic kidney; HCV, hepatitis C virus; LC, liver cirrhosis; PBC, primary biliary cirrhosis.

significantly higher in the LT recipients during the critical phase (i.e., from the initial to postoperative one week).

Several population factors affect the IA titers. Among them, age is a well-known factor that affects

the IA titers. Infants produce IA at 3~6 months. The titer reaches the maximum at the age of 5~10 years. In subjects aged 80 years or more, the IA titers show a progressive decrease with age [5]. Gender can also influence the IA titers. The IA titers are

Fig. 2. Serial changes in (A) IgG and (B) IgM anti-donor isoagglutinin titers and (C) CG (total protein-albumin) levels in KT and LT recipients. The LT recipients showed higher IgG IA titers than the KT recipients from before transplantation to one week after transplantation. On the other hand, the IgM IA titer did not show a significant difference between the KT and LT recipients except one week after transplantation. Abbreviation: CG, calculated globulin; KT, kidney transplantation; LT, liver transplantation; IA, isoagglutinin.

higher in females than in males [5]. Differences in age, gender distribution, and induction therapy might have contributed to the differences in IA titers between the KT and LT recipients (Table 1). The

number of plasmaphereses to reach the target anti-donor IA titer can be estimated based on the initial IA titer [16,17]. Kim et al. suggested a linear relationship between the initial IA titer and the num-

Fig. 3. Linear regression and correlation analyses for the relationship between (A) IgG or (B) IgM anti-donor isoagglutinin titer and CG (total protein-albumin) level. Abbreviation: CG, calculated globulin.

ber of PP ($y=0.6829x+0.0523$, $R^2=0.946$) [18]. On the other hand, there was no difference in the IA titer between the two groups from postoperative four weeks.

The globulin status before and after transplantation might be a factor that affects the IA titer. The compensatory increase in globulin due to the decreased albumin level is a common finding in chronic liver failure [19]. The marked polyclonal increase in globulin may contribute significantly to oncotic pressures. In the present study, the IgG and IgM IA titers showed positive correlations with the CG levels (Fig. 3). The globulin levels can change according to the type of liver disease. For example, in primary biliary cirrhosis, the IgM level is increased considerably. IgG is increased in chronic active hepatitis, whereas IgA is increased in portal cirrhosis [20]. The underlying disease of LT patients in this study was mostly LC with or without a hepatitis C viral infection (65.6% and 21.9%, respectively), as

shown in Table 1. This disease composition might have led to the high IgG IA titer in LT patients. The increased globulin level decreased significantly immediately after LT and decreased further several days after LT, reaching levels comparable to healthy individuals [21,22]. Similarly, the CG level was significantly higher in the LT recipients initially. After transplantation, however, there was no significant difference in the CG level between the LT and KT recipients (Fig. 2C). Compared to the immediate change in CG difference after transplantation, the difference in IA titer lasted for up to one week. Although RTX significantly affected IgM depletion in both KT and LT [23], differences in B cell deposition patterns were reported. In LT, IgM secreting B cells remained detectable for one week after RTX and reappeared after six months. On the other hand, they were depleted after RTX and not detected in the first year in KT [23]. The study was designed to analyze the data collected for therapeutic pur-

poses, including only anti-donor IA levels after ABOi transplantation. After ABOi transplantation, the anti-donor IAs can react with the ABO antigens expressed in graft endothelial cells and affect the IA levels in the patient's serum. In addition, plasma cells that do not respond to the RTX treatment can affect the IgG IA levels.

IA antibodies are produced upon contact with bacterial or food antigens during early infancy. Naturally occurring IA antibodies are predominantly IgM produced in a T cell-independent manner [24]. In type O individuals, however, IgG is also produced in a T cell-dependent manner by the adaptive immune system [6,25] and activated B cells of this manner that have developed to plasma cells and memory B cells. Various IA titration methods, such as the saline tube method, AHG tube method, and LISS-Coombs column agglutination methods, have been used to evaluate these IgM and IgG IA levels [3,12,26-31]. At the authors' institute, the IgM IA levels and IgG IA levels were titrated using the saline tube method and DTT-AHG tube method, respectively. In Fig. 2, the initial median IgG IA titer was 8.0 (1:256) in the KT recipients and 9.0 (1:512) in the LT recipients. These results were different from a previous study reporting that ABOi KT recipients had a median IgG IA titer of 1:64 initially [30]. The initial IgM IA titer of the KT and LT recipients in the present study was 6.0 (1:64), which is similar to the results of previous reports (1:8~1:64) for group O Koreans [32,33]. The IA titration method can cause an IA titer discrepancy [27,34]. A standardized method is needed for IA titrations because the IA titer is associated with the prognosis of ABOi transplantation [35].

This study had several limitations. First, the total IgG and IgM levels were not determined. Higher IgG IA of LT recipients in this study was assumed to be a part of the polyclonal increase in globulin in LT recipients. The CG level was used as indirect evidence of the globulin status. On the other hand, the CG level was not the exact globulin level. Second, the non-anti-donor IA titer was not determined after ABOi transplantation because only the anti-donor IA was considered to have clinical importance. A comparison of the anti-donor and non-anti-donor IA titers will be needed to evaluate the immune responses in ABOi transplantation properly. Finally, the titers were not classified and analyzed according to the underlying disease or immunosuppressive regimen. The possibility that immune diseases, such as systemic lupus erythematosus and primary biliary cirrhosis, will affect the IA titer cannot be excluded. Although the induction therapy and maintenance regimens of the patients enrolled in the study were similar, further research will be needed to determine if the IA titer changes differ according to the immunosuppressants [36,37].

In conclusion, type O LT recipients showed higher initial IgG IA titers than the type O KT recipients. This higher titer in type O LT recipients persisted during the critical phase (from before transplantation to postoperative one week). Therefore, the difference in IA titer between the underlying diseases should be considered in a desensitization protocol before ABOi SOT.

요약

배경: ABO 부적합 고형 장기이식의 경우, 이식

전과 이식 후 2주 사이에 공여자에 대한 ABO 동종응집소를 최소화하고 관리하는 것은 초급성 거부반응을 방지하기 위해 중요하다. 동종응집소 역가에 영향을 미칠 수 있는 몇 가지 요인들이 보고되어 왔으나, 이 연구는 처음으로 신장 이식과 간 이식 환자 사이에 동종응집소 역가의 차이가 있는지 여부를 평가하였다.

방법: 2013년 3월부터 2018년 3월까지 ABO 부적합 이식을 받은 38명의 신장이식, 32명의 간이식 O형 수혜자가 분석에 포함되었다. 신장이식 및 간이식 수혜자에서 이식 전, 이식당일, 수술 후 1주, 4주, 그리고 1년에 측정된 IgM 및 IgG 동종응집소 역가를 평가하였다.

결과: 간이식 수혜자가 신장이식 수혜자보다 이식 전 IgG 동종응집소 역가가 높았다($P=0.01$). 간이식 수혜자의 더 높은 동종응집소 역가는 이식 전부터 수술 후 1주까지의 주요기간 동안 유지되었다. 수술 후 4주에는 신장이식과 간이식 수혜자간 IgG 및 IgM 동종응집소 역가에 유의한 차이가 없었다.

결론: 기저질환에 따른 동종응집소 역가의 차이가 ABO 부적합 고형 장기이식 전 탈감작 프로토콜에 고려되어야 한다.

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