Editorial

ABO incompatibility as a possible risk factor for hepatic artery thrombosis in living donor liver transplantation

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Living donor liver transplantation (LDLT) has been especially important in eastern countries, where a scarcity of donors for deceased donor liver transplantation (DDLT) has adversely affected the treatment of end-stage liver diseases. Even in western counties, however, LDLT has been an important approach to overcoming donor shortages. There are several difficult technical aspects of LDLT compared to DDLT using whole liver grafts, mainly because LDLT employs a partial liver graft with small and short vascular structures, and hepatic arterial thrombosis (HAT) is one of the most severe complications after LT in the recipient, and generally more after LDLT than that after DDLT, especially in pediatric cases (1). Actually, in our experience in Nagasaki University, of total 309 LT cases (LDLT, 293; DDLT, 16), 10 cases (3%) developed HAT all of which after LDLT.

Other reported non-surgical causes of HAT include intimal injury of the recipient hepatic artery due to previous intraarterial treatment for hepatocellular carcinoma (2), prolonged ischemic time (3), cytomegalovirus infection (4), and specifically in cases of LDLT, ABO incompatibility (ABOi) between the donor and recipient (5).

In LDLT, because of the limitation of the relationship between the donor and recipient, ABOi transplantation is considered a treatment option and one of the most challenging matters to overcome, and several step-by-step innovations have made ABOi-LDLT a realistic modality by making patient/graft survival nearly comparable to that in ABO-compatible LDLT (6). These innovations include two major breakthroughs. The first was the use of a local infusion therapy generally including three drugs (steroid, protease inhibitor, prostaglandin E1) via a catheter placed in the portal vein (7) and/or hepatic artery (8), and the second was desensitization with rituximab (7). Rituximab is an anti-CD20 antibody originally introduced to treat B-cell lymphoma, and can absolutely eliminate B lymphocytes before transplantation. These breakthroughs have rendered unnecessary several other strategies of ABOi-LDLT, including plasma exchange (9), splenectomy (10), and even local infusion therapy (11).

Theoretically, ABOi can be a non-surgical risk factor for HAT in liver transplantation, because the blood cells of the donor can remain in the liver even after perfusion, and A or B antigens are also expressed on the surface of the endothelium of the vessels (12). Both the remaining blood cell and endothelium might induce an antibody-mediated reaction that could lead to hemagglutination. In fact, several papers showed that ABOi was a risk factor for thrombotic microangiopathy (TMA) after LDLT, possibly because of antibody-mediated hemagglutination (13), as the one possible mechanism of disseminated intravascular coagulation (DIC). As mentioned above, local infusion therapy was introduced to avoid not only the immune reaction itself, but also the subsequent "intrahepatic DIC", which can cause a disturbance of microcirculation in the liver, by using protease inhibitor and prostaglandin E1.

Since the introduction of rituximab, antibody-mediated rejection has been very well controlled, and local infusion therapy has finally been abandoned in many centers. However, an additional concern was introduced by Dada and colleagues—namely, the potential development of venous thrombosis due to acute hypersensitivity reaction with rituximab for B-cell lymphoma (14). On the other hand, Diószegi *et al.* demonstrated the efficacy of rituximab for microthrombotic renal involvement in systemic lupus erythematosus by controlling the antibody-mediated reaction (15). According to these papers, it is important to avoid the infusion reaction with rituximab itself, and as long as hypersensitivity does not occur, rituximab might prevent thrombosis.

In the current article by Kim *et al.*, they showed that ABOi-LDLT has no adverse impact on the incidence and treatment of HAT using a rituximab-based desensitization protocol (16), same as our experience [1/53 (1.9%) in ABOi *vs.* 9/240 (3.8%) ABO identical/compatible LDLT]. Accordingly, the efficacy of rituximab to control the antibody-mediated reaction might be sufficient to prevent subsequent possible hemagglutination in ABOi LDLT, but the transplant physician should be aware that possible antibody-mediated TMA or diffuse biliary ischemic damage have been reported specifically in ABOi LDLT, even in the rituximab era (17). A prospective multicenter study with a sufficient number of cases is merited to definitively resolve this matter, as Kim *et al.* also mentioned.

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Footnote

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