ABO-Incompatible Liver Transplantation

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45.1 Introduction

"Organ demand versus supply" is the greatest obstacle to increase the frequency of liver transplantation, which has been one of the medical breakthroughs in recent times. Transplantation across the ABO blood groups is discouraged because of the risk of acute rejection, graft loss, and a poor outcome; thus, it is generally used only in emergency situations. In living-donor liver transplantation (LDLT), donor selection is restricted to family members, and ABO-incompatible (ABO-I) liver transplantation becomes inevitable as a means to breach this obstacle. This has compelled transplant surgeons to devise innovative strategies, such as local infusion therapy and rituximab, to prevent complications in ABO-I liver transplantation. However, with an increased risk of infection, antibody-mediated rejection, and consequent vascular and biliary complications, ABO-I liver transplantation continuous to be a formidable challenge in LDLT. In this review, we study the past and current immune strategies adopted by centers across the world for ABO-I LDLT, to provide insight for change or modification so as to improve outcomes and reduce ABO incompatibility-related complications in LDLT.

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45.2 History of ABO-I Liver Transplantation

Since its inception by Thomas Starzl, ABO-I liver transplantation has evolved through an era of controversy and immunological violation to the current inevitable phase. The initial animal experiments conducted by Starzl demonstrated that the liver is "a privileged organ" with much greater resistance to acute rejection than the kidney or heart. With this understanding, Starzl breached ABO blood group barriers, particularly in the emergency situations when given no choice but to proceed with first available organ. In 1979, Starzl's group reported 11 human ABO-I liver transplantations without evidence of acute rejection. During this period, ABO incompatibility was not considered a contraindication to liver transplantation. In fact, ABO-I grafts were used children because of the difficulty of finding compatible small grafts, and in adults during emergencies. In 1986, Gordon et al. [1] reported 31 ABO-I liver transplants, carried out using cyclosporine and prednisolone for immunosuppression, and found that graft survival in the ABO-identical group was significantly better than that in the ABO-compatible and -incompatible groups. In children, he used ABO-I grafts in emergency as well as in elective conditions because of the shortage of small grafts. As the 1-year graft survival rate in adults was acceptable, he advocated the use of ABO-I grafts in

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adults only in emergency situations. Furthermore, Rego et al. [2] reported hyperacute rejection after ABO-I liver transplant, despite the "privileged" status of the liver. In 1989, Gugenhein et al. [3, 4] confirmed lower graft survival and hyper-acute rejection in ABO-I liver transplantation. In their series of 17 ABO-I liver transplants, Gugenhein et al. postulated immunological damage as the cause of low graft survival and reported antibody-mediated rejection as a cause of graft failure in six patients. They also acknowledged an increased incidence of arterial thrombosis and progressive cholangitis in ABO-I grafts. The debate continued about the increased incidence of complications of ABO-I liver transplants. In a control matched study including 15 ABO-I liver transplants, Sanchez-Urdazpal et al. [5] confirmed an increased incidence of cholangitis, bile leak, cellular rejection, and hepatic artery thrombosis in an ABO-I group. Because of the high incidence of complications, ABO-compatible liver transplantation became unpopular and was reserved for emergency transplant only.

45.3 Need of ABO-I Transplant in Setting of Living Donor

Since the donor of an LDLT is usually a first-degree relative, limiting choice, the use of grafts across the ABO blood groups is often inevitable. This has forced transplant surgeons to adopt various innovative methods to prevent the complications associated with ABO-I liver transplantation. In the early 1990s, various centers reported [6–8] improved the results of ABO-I liver transplantation in children by using pre- and postoperative plasma exchange and OKT-3. We have learned much from the experience of ABO-I kidney transplant surgeons who used peri-operative plasma exchange, splenectomy, and high-dose immunosuppressive drugs to ensure the success of ABO-I transplantation. Anti-donor antibody-induced complement fixation and endothelial damage leading to hemorrhagic necrosis by the formation of micro-thrombi in the graft vasculature is a major cause of early graft failure [9]. Diffuse intra-organ coagulation (DIC) can be confirmed by C4D immunofluorescent staining. To overcome this "single organ DIC," Tanabe's group from Keio University, Japan, endorsed portal vein infusion with prostaglandin E1, methylprednisolone, and gabexate mesilate [10]. Prostaglandin E1 improves microcirculation through vasodilatation and the prevention of platelet thrombi. Gabexate mesilate is a protease inhibitor that inhibits platelet aggregation and coagulation factors. Nakamura et al. [11] used a hepatic artery infusion of prostaglandin E1 to prevent biliary complications and improve the bile duct blood supply. In 2003, Monteiro et al. [12] gave rituximab (anti-CD20 monoclonal antibody) to a 15-year-old boy undergoing emergency ABO-I liver transplantation for resistant B cell lymphoma to reduce anti-donor antibody-producing B cells.

45.4 Current Strategies for ABO Incompatibility in LDLT Worldwide

ABO-I LDLT strategies are directed at eliminating or reducing the anti-ABO antibody. Apart from the routine immunosuppression given to all liver transplant patients, the following methods are also used in ABO-I LDLT.

45.4.1 Rituximab

Rituximab is the monoclonal chimeric human anti-CD20 antibody that revolutionized ABO-I LDLT. CD20 is expressed in most of stages of B cell development but not in plasma cells or stem cells. Rituximab was approved for resistant B cell lymphoma at a dose of 375 mg/m^2 weekly for 4 weeks. To deplete normal B cells in an ABO-I recipient, a single dose of rituximab is considered enough. In ABO-I liver transplantation, the timing of giving rituximab varies among centers from 7 to 15 days preoperatively. Today, most knowledge of the pharmacodynamics of rituximab comes from its use in B cell lymphoma. However,

Genberg et al. [13] recently studied the pharmacodynamics of rituximab in a renal transplant recipient. They found that a single dose of rituximab (375 mg/m2) was sufficient to completely eliminate B cells from the peripheral blood. Although reduced numbers of B cells were seen in the peripheral blood as early as 3 days after rituximab administration, complete elimination was seen only after 3 weeks. Nevertheless, a single dose of rituximab is not enough to completely eliminate B cells from the lymph node. These remnant cells became activated after antigen exposure from the graft and produced the anti-ABO antibody. The value of the complete elimination of B cells needs to be balanced against the need for 2–3 years of prolonged immunosuppression caused by 375 mg/m2 of rituximab. Conversely, the initial 4–6 weeks is critical for antibody-mediated rejection, and B cell suppression is required only for this period. Therefore, the ideal dose of rituximab remains unresolved.

45.4.2 Plasmapheresis

Anti-ABO antibodies are the trigger for antibody-mediated rejection after ABO-I LDLT. Thus, the anti-ABO antibody titers are reduced preoperatively by plasma exchange, plasma filtration, or immune adsorption in most centers across the world, aiming for immunoglobulin M and immunoglobulin G titers below 1:16 at the time of transplantation to prevent antibody-mediated rejection. These titers are maintained at these values because increasing antibody titers in the early postoperative period are associated with rejection. Plasmapheresis is the most effective way to control humoral antibody response to prevent rejection.

45.4.3 Mycophenolate Mofetil

Mycophenolate mofetil is a functionally selective drug that is cytotoxic to B and T lymphocytes. Since rituximab is ineffective against the plasma cells with active B cell-producing antibody, mycophenolate mofetil has been incorporated in a protocol used by groups from Chicago, Tohoku, Tokyo, Yokohama, and Italy. The preoperative administration of mycophenolate mofetil reduces plasma cells in the circulation.

45.4.4 Intravenous Immunoglobulin (IVIG)

Intravenous immunoglobulin causes FC-receptor-dependent B cell apoptosis and inhibits complement- and T cell-mediated allograft injury. A recent trial at Kyushu University, Japan, involving 30 patients showed the efficacy of IVIG given with rituximab and plasma exchange. Intravenous immunoglobulin is very promising in emergency ABO-I LDLT, when there is insufficient time for the action of rituximab. Cost is the major limiting factor in IVIG treatment.

Since the introduction of rituximab, the need for splenectomy in ABO-I LDLT is questionable. Raut et al. [14] showed no difference in anti-ABO-antibody response between a splenectomy group and a non-splenectomy group. In past local infusion of prostaglandin E, methylprednisolone, 1and gabexate mesilate, 1 through the portal vein or hepatic artery was used.

45.5 Outcomes and Long-Term Survival After ABO-I Liver Transplant

In meta-analysis by Lee et al. involving 8000 ABO-I liver transplant found, cases that used rituximab in ABO-I LT patients showed better 1-year graft survival after ABO-I LT than those that did not use rituximab. Furthermore, in patients with preoperative Rituximab 1-, 3-, and 5-year graft survivals of ABO-I LT were comparable to those of ABO-C LT. On the other hand, biliary stricture and ACR tended to be more prevalent after ABO-I LT when rituximab was not used. There were no differences in AMR and patient survival in accordance with the use of rituximab.

Key Points

- ABOI liver transplantation have become inevitable in this era of limited organ supply.
- Rituximab—The monochrome anti-CD20 antibody depletes the normal B cells in the ABOI recipients.
- Anti-ABO antibodies are removed by plasmapheresis.
- Mycophenolate reduces plasma cells in circulation.
- IVIG reduces compliment and T cells mediated allograft injury.
- Prostaglandin improves micro circulation and prevent platelet thrombus formation.

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