Evading antigens—ABO-incompatible liver transplantation

Ali Zarrinpar and Ronald W. Busuttil

Whereas the status of the liver as a privileged organ has now become the greatest obstacle to liver transplantation during transplantation have continued. Previously restricted to paediatric patients and emergencies, advances in immunosuppression protocols have improved outcomes to the point that ABO-incompatible liver transplantation might be more widely used in adults.

Following advances in surgical technique and the perioperative care of patients with end-stage liver disease, the supply of suitable grafts has now become the greatest obstacle to liver transplantation. In the absence of the technology to generate organs ex vivo, dependence on the donor pool has resulted in various attempts to broaden its limits. These attempts include modest expansions in donor numbers through increasingly aggressive organ utilization: living donors, deceased donor split-livers and extended criteria donors. With the expansion come the attendant risks, whether they are poor initial graft function or increased biliary and vascular complications. Despite all these efforts, graft options continue to be limited in many instances. One avenue that has been explored since the initial development of liver transplantation by Starzl is transplantation across ABO blood groups, which has been addressed again in the current series published by Song et al.¹

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The status of the liver as a ‘privileged organ’ that is resistant to rejection led to the breaching of the blood group barrier early during the history of liver transplantation.² Although graft survival rates in ABO-incompatible (ABOi) liver transplant recipients were worse than in ABO-compatible (ABOc) ones, they were deemed acceptable with six of 11 patients surviving longer than 6 months. Because of this result, Starzl and others advocated the limited use of ABOi liver transplantation in children, owing to the shortage of suitable grafts, and in adults during emergency situations when time is of the essence. Starzl and colleagues later published their experience with 31 ABOi liver transplantsations using ciclosporin and prednisolone for immunosuppression and found the results “surprisingly successful”; although they continued to advocate severely limiting incompatible grafts.³

As the worldwide experience with liver transplantation grew, more groups found ABOi liver transplantation to be fraught with hyperacute rejection and antibody-mediated rejection resulting in graft loss, cholangitis, cellular rejection and arterial thrombosis.⁴ This development led to a period of unpopularity, though not without continued innovations in recipient management. Incremental changes in immunosuppression resulted in gradual improvement of outcomes. Lessons learnt from ABOi renal transplantation and techniques such as perioperative plasma exchange, splenectomy and immunosuppression with tacrolimus and muromonab-CD3 (also known as OKT3) were incorporated.⁵ Other advances also helped. For instance, prostaglandin E1 (PGE1) hepatic artery infusions can be used to provide vaso-dilation, improve microcirculation, inhibit platelet thrombi formation and, therefore, enhance bile duct blood supply.⁶ Gabexate mesilate, a serine protease inhibitor of platelet aggregation and coagulation factors, was used in combination with PGE1 and methylprednisolone as an intraportal vein infusion to keep anti-donor blood group antibody titres low and inhibit rejection or vascular complications through the postoperative course.⁷ Perhaps the most important development was the introduction of rituximab, an anti-CD20 monoclonal antibody, previously used for the treatment of lymphoma, post-transplantation lymphoproliferative disorder, rejection and then positive crossmatch kidney transplantation. A research group at the University of Medicine and Dentistry of New Jersey first used a combination of rituximab, plasmapheresis and splenectomy in a 15-year-old patient who received an ABOi liver transplant for fulminant hepatic failure with good long-term results.⁸ This approach ushered in similar applications of rituximab in adult living donor liver transplantation.⁹ Protocols for ABOi liver transplantation aim to reduce or eliminate anti-ABO antibodies. Standard transplantation immunosuppression is therefore supplemented by a combination of plasmapheresis, splenectomy, hepatic and/or portal infusion, rituximab, basiliximab, mycophenolate mofetil and intravenous immunoglobulin. Given the numerous possible permutations of additional immunosuppressive treatments and the infrequent circumstances under which ABOi liver transplantation occurs, it becomes difficult to optimize a treatment combination that minimizes rejection episodes and infection risks.
Song et al., however, have actively pursued a rituximab desensitization protocol since 2008 and have been optimizing the protocol since then. For 2–3 weeks before transplantation, recipients receive a single dose of rituximab followed by plasmapheresis a week later, with the goal of bringing recipient isoagglutinin (IA) titres down to ≤1:8. Initially, they used local graft infusion with methylprednisolone and PGE1 through the hepatic artery or portal vein for 3 weeks, as well as 1 week of cyclophosphamide; but the latter modality was eliminated after some adverse effects. After transplantation, immunosuppression consisted of a standard combination of tacrolimus, steroids and mycophenolate mofetil. Splenectomy, initially avoided owing to concerns of infection risk, was later incorporated in an attempt to decrease the risk of antibody-mediated rejection.

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This largest single-centre series of ABOi liver transplantation with 235 recipients mainly reported two major findings. Firstly, and most importantly, Song et al. have arrived at an ABOi liver transplantation immunosuppression protocol with rates of overall and graft survival that are comparable to the ABOc group. The ABOi group did have more biliary complications and more antibody-mediated rejection (defined as periportal oedema and necrosis or haemorrhagic oedema associated with an increase in IA titres, in addition to ≥50% stromal-positive portal tracts staining for C4d, a degradation product of the complement pathway). Antibody-mediated rejection was treated by increasing the dose of tacrolimus and steroids and by performing plasmapheresis until IA titres decreased to ≤1:32 and stabilized. Patients who were resistant to this initial treatment received high-dose intravenous immunoglobulin and a steroid bolus, along with daily plasmapheresis. The second important finding is that although splenectomy and local graft infusion therapy do not decrease the rate of antibody-mediated rejection when added to rituximab, they seem to increase the infection risk. This observation is in agreement with evidence from a multicentre study conducted in Japan, which found only rituximab to be efficacious.

In conjunction with previous series, Song and colleagues seem to have cemented the role of rituximab in ABOi liver transplantation. This conclusion is the culmination of the dedicated effort of selected centres with the technical and medical expertise to pursue this goal and the required patient population. The paper provides further impetus to translate these findings to the treatment of antibody-mediated rejection. The question remains, however, whether this achievement will affect worldwide practice outside areas where living donation is the dominant source of grafts. One major issue is the need for a 2–3 week pre-transplantation desensitization, not practicable for deceased donation. The other issue is that ABOi transplantation does not truly increase the overall donor pool; it only makes it more fluid. Even if we ignore the cost of desensitization and the increased risk of biliary complications and antibody-mediated rejection, because deceased donor transplantation is a zero-sum game, an increase in ABOi liver transplantation would decrease the number of the superior ABOc transplantations. Despite improved outcomes, just as Dr Starzl stated 40 years ago, ABOi transplantation should be limited to those for whom ABOc transplantation is not an option.


