ABO incompatible liver transplantation

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Disclaimer

Off label use of Rituximab will be mentioned

How we see nephrologists

How we are seen
Background

- A and B antigens are present on many cell types and are secreted in some body fluids.

- The genes responsible for the synthesis of the ABO molecules are highly conserved among animals and even some plants, and this indicates that these molecules must have some important functional significance.

- However, the evolutionary advantage and precise function of these antigens remain unknown.

- Why individuals develop antibodies to the A or B antigens in not clear as in evolutionary terms, exposure to these non-self blood type antigens has no reason to occur.

- Human newborns do not have antibodies to blood group antigens, and children develop these antibodies to epitopes that resemble A and B glycoproteins in food and after exposure to bacteria (GIT).
Background

• Blood group antigens are expressed in almost every cell in the body, and an individual develops antibodies against blood group antigens (anti-A/B antibodies) absent in his or her own tissue.

• Grafts expressing foreign A/B antigens are usually hyperacutely rejected.

• For a long time, it was considered medical malpractice to neglect the blood group system during cadaveric transplantation.

• Because there are far more patients waiting for organs than organs available, a variety of attempts have been made to transplant AB0-incompatible (AB0i) grafts.

• Most AB0i LTs have had a lower graft survival rate due to hepatic arterial thrombosis, various episodes of biliary complications or acute rejection.

ABMR pathogenesis

FIG 3 UNOS 1987-2016 deidentified patient-level data. (A) Overall adult survival stratified by donor/recipient blood type relationship in LT (ABO-ILT versus ABO-CLT). (B) Overall pediatric survival stratified by donor/recipient blood type relationship in LT (ABO-ILT versus ABO-CLT). y axis: percentage recipient survival of total recipients. x axis: years after LT.
The rules

• The durable survival of AB0i solid organ allografts seems to be primarily dependent on 3 conditions:

• the low expression of antigen on the graft, as in case of A2 positive organs.
• a low titer of anti-donor AB0 antibodies in the recipient before transplantation. ?? Do not attempt with titres > 1:64.
• and the ability to maintain low titers of antidonor AB0 antibodies in the recipients after transplantation, at least for the first 3 to 6 weeks.

Two regimens were designed based on isoagglutinin IgG and IgM titers:

- When isoagglutinin IgG and IgM titers were 64, liver transplantation was directly performed and rituximab (375 mg/m2) was administrated on postoperative day 1 (regimen I).
- When isoagglutinin titers were >64, rituximab (375 mg/m2) was administered preoperatively with or without plasmapheresis and boosted on postoperative day 1 (regimen II).

Immunosuppression was achieved by administration of mycophenolate mofetil, tacrolimus, and steroids.

1-, 3-, and 5-year survival rates were 81.7%, 75.7%, and 71.0%, respectively, for ABO-incompatible LDLT recipients, compared to 81.0%, 75.2%, and 71.5% for ABOC recipients.
Techniques used (DCD OLT)

• Apharesis-
  • TPE
    • With TPE, usually 1.2 times (1.0-1.5) the patient’s plasma volume is treated. The amount of treated plasma volume correlates with the removal of 63% to 72% of the original plasma constituents. At the end of a TPE procedure, IgM is very low. High levels of IgM are usually reduced with one or two TPE.

• Double filtration TPE
  • The Evaflux2A (Kawasumi laboratories, Japan) eliminates IgG as well as IgM. After processing 1000 mL plasma, the ratio of solute returned to the patient, or the sieving coefficient, is 0.00 for IgM and 0.19 for IgG. As the value of 0.00 for IgM indicates, these pore-based filter columns are most effective for IgM depletion. The target iso-titer < 1:16 was reached with only 4 treatments, even in cases with very high initial iso-titers (> 1:2048)

Techniques used (DCD OLT)

• Immunoadsorption
  • Two methods-
    • (GlycosorbAB0, Glycorex Transplantation, Lund, Sweden). This technique is preferred to reduce the iso-titer. Because the IA-column is highly selective for anti-A/B antibodies, other antibodies are not affected and no replacement fluid is required. With each plasma volume treated with Glycosorb, the iso-titer of IgG and IgM is reduced by one titer. Compared to the baseline, a reduction to 59% for IgG iso-titer and to 30% for IgM iso-titer is considered average.
    • Semiselective antibody removal (Immunosorba, Globaffin, Fresenius Medical Care). These columns mainly bind IgG and, to a lesser degree, IgM, regardless of their specificity. This unspecific removal is beneficial for transplant candidates with an additional sensitization. In AB0i kidney transplant patients, a single session of IA decreased anti-A/B IgG iso-titers more effectively than antigen-specific apheresis. IgG was reduced to 28% of the baseline value and IgM to 74%.

Techniques used (DCD OLT)

• **IVIG**-
  - Block Fc receptors on mononuclear phagocytes and directly neutralize alloantibodies. They also inhibit the expression not only of CD19 on activated B cells and the complement system but also of alloreactive T cells.
  - Hanto *et al* [44] compared AB0i recipients receiving TPE and IVIG with patients receiving only TPE during the post-transplant period. In this study, the patient group with IVIG did not develop AMR, but 27.3% of the patients in the other group did develop AMR post-transplant.
  - Unfortunately, a transient increase of anti-A/B titers is observed after IVIG administration due to the passive transfer of anti-A/B. Thus, IVIG should not be administered prior to AB0i LDLT (and will also make monitoring tricky).

Splenectomy

• Several reports have shown that splenectomy does not offer any immunological advantage in AB0i LDLT. For example, Raut et al. observed no statistically significant differences in anti-A/B IgM and anti-A/B IgG titers between “splenectomy” and “non-splenectomy” groups.

• An exception to this general rule are patients with imminent “small for size” syndrome, who have better outcomes after splenectomy (Avoid graft-to-recipient body weight ratio > or = 0.8% or graft weight ratio > or = 30%).

Immunosuppresion

• The past-
  • In 1998, Tanabe et al, described a new protocol in which they, in addition to perioperative TPE and splenectomy, supplemented systemic immunosuppression with portal vein infusion therapy (PVIT). Methylprednisolone, prostaglandin E1 and gabexate mesilate were used in the PVIT - Tanabe M, et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible transplantation. Transplantation 2002; 73: 1959-1961 [PMID: 12131697]

• Now-
  • Many centres use quadruple immunosuppression: Monoclonal antibodies, calcineurin inhibitors, antimetabolites and steroids.

Monoclonal Ab’s

• Rituximab –
  • Anti-CD20 antibody that depletes B cells. It acts by complement- and antibody-dependent cell-mediated cytotoxicity.
  • The CD20 antigen is expressed on pre and mature B cells, but not on long living plasma cells persisting in the bone marrow. Hence, rituximab does not directly affect antibody-producing plasma cells.
  • A single dose of rituximab in AB0i LDLT suppresses B cells for more than six months after transplantation in the peripheral blood.
  • However, because B cells in the lymph node are unaffected, they are activated by the AB0i graft, and the anti-A/B titers rise for the first four to six weeks after transplantation.
  • ?No role for addition of basiliximab.

Accommodation

• The term “accommodation” comes from the first experiences in the 1980s with a surviving renal graft in cases of ABO incompatibility. ABO incompatibility induces a hyperacute rejection of the kidney graft which can be prevented by eliminating the anti-ABO haemagglutinins in the recipient prior to the transplant.

• With ABOi circulating erythrocytes are almost 100% lysed, but not the case with endothelial cells, i.e., they must have some “protective” factors.

• Once the hyperacute rejection is overcome, the kidney graft can “accommodate”. Despite widespread use of the term, the mechanisms responsible for accommodation are still largely unknown even today.

Accommodation

• In addition to membrane antigens, there are soluble A and B epitopes bound to the circulating von Willebrand (vW) factor.

• This fraction of circulating A and B antigens is largely released by endothelial cells.

• Transplanting A2 kidneys in O recipients has good results, and the A2 subtype is precisely the one that correlates to an absence of A antigen bound to the vW factor in blood, so modulation of binding might be involved in accommodation.

The presence of c4d in renal biopsies of a normal ABO-compatible allograft is associated with alloantibody formation and humoral rejection with a very poor prognosis.

Surprisingly, the presence of these deposits in ABO-incompatible transplants is associated with accommodation, rather than with rejection of the graft.

One possible explanation is that C4d reflects the activation of the complement that does not manage to generate the membrane attack complex C5-9.

On the other hand, activation of complement induced by the union of group A or B epitopes bound to the vWfactor and released by endothelial cells would generate complement factors (C1q, iC3b, C5L2) with anti-inflammatory capabilities and the ability to suppress antigen presentation and the activation of T cells.

Conclusions

• ABOi is much more mainstream
• ABOi LT have comparable survivals with more biliary complications
• Caution with anti A and B titres pretransplant
• In terms of cost – Membrane TPE is effective and minimal anti CD20 is required