ABO incompatible liver transplantation

Prof G Paget

Wits/CMJAH/DGMC

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).

Richard B. Freeman Jr. Overcoming the ABO Incompatibility Barrier. LIVER TRANSPLANTATION 15:831-833, 2009.

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.

Silke Rummler, et al. Current techniques for AB0-incompatible living donor liver transplantation. World J Transplant 2016 September 24; 6(3): 548-555

ABMR pathogenesis

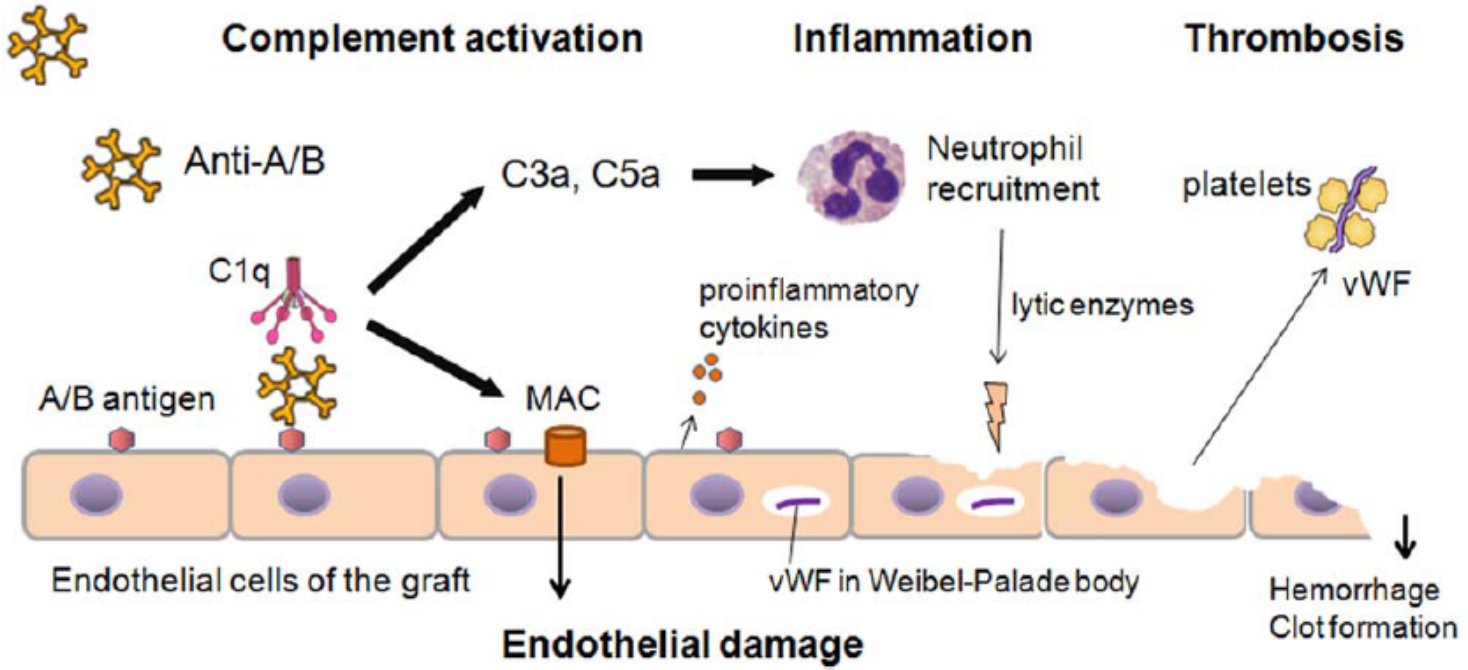

FIG 2 Proposed mechanism of hyperacute rejection in ABOi organ transplantation. Abbreviation: MAC, membrane attack complex; vWF, von willebrand factor. Adapted with permission from *Understanding the Complexities of Kidney Transplantation.*[6] Copyright 2011, InTech.

Matthew B. Goss, and Abbas Rana. ABO-Incompatible Liver Transplantation: Is It a Viable Option With Modern Innovation? CLINICAL LIVER DISEASE, VOL 10, NO 5, NOVEMBER 2017

Epidemiology

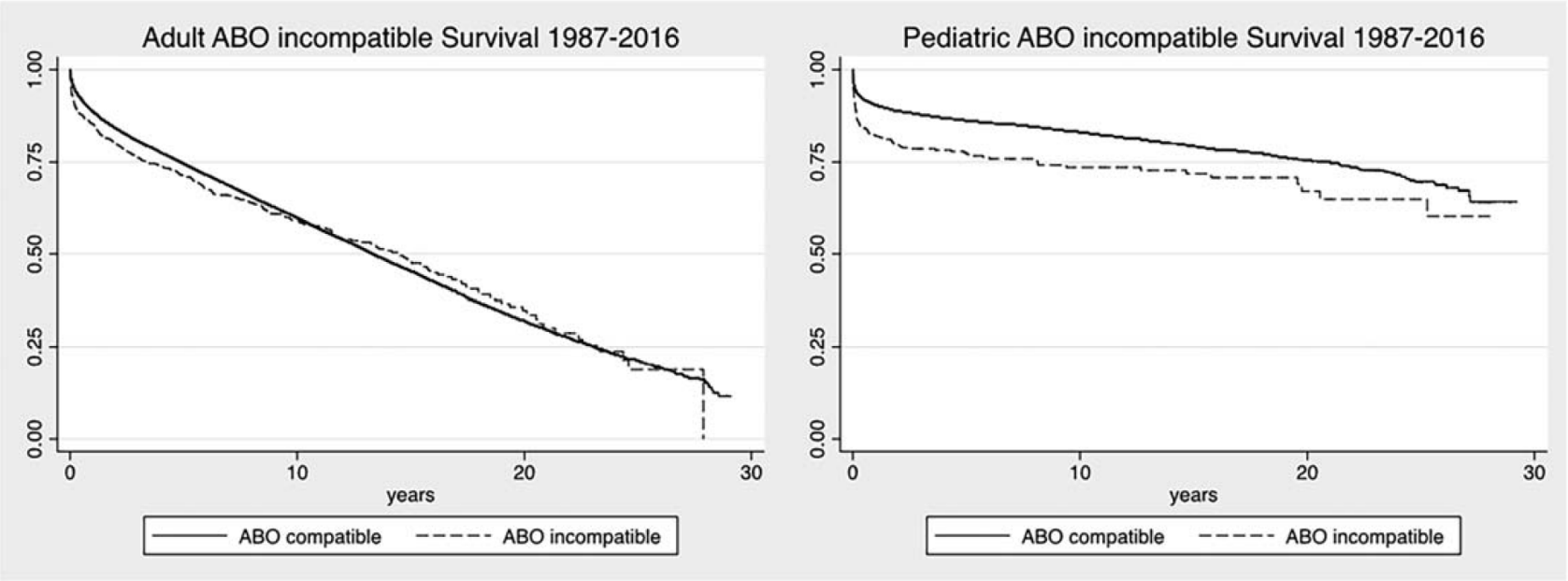

FIG 3 UNOS 1987-2016 deidentified patient-level data. (A) Overall adult survival stratified by donor/recipient blood type relationship in LT (ABO-ILT versus ABO-CLT). (B) Overall pediatric survival stratified by donor/recipient blood type relationship in LT (ABO-ILT versus ABO-CLT). *y* axis: percentage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

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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.

Warner PR, Nester TA. ABO-incompatible solid-organ transplantation. Am J Clin Pathol 2006; 125 Suppl: S87-S94 [PMID: 16830960 DOI: 10.1309/8w4x9h6f8ftlcgyx]

Techniques used (LD OLT)

- 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

Chen-Fang Lee, et al. Adult Living Donor Liver Transplantation Across ABO-Incompatibility. Medicine Volume 94, Number 42, October 2015

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)

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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%.

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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* 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).

Hanto DW, Fecteau AH, Alonso MH, Valente JF, Whiting JF. ABOincompatible liver transplantation with no immunological graft losses using total plasma exchange, splenectomy, and quadruple immunosuppression: evidence for accommodation. Liver Transpl 2003; 9: 22-30 [PMID: 12514769 DOI: 10.1053/jlts.2003.50011]

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%).

Raut V, Mori A, Kaido T, Ogura Y, Taku I, Nagai K, Sasaki N, Endo K, Hata T, Yagi S, Egawa H, Uemoto S. Splenectomy does not offer immunological benefits in ABO-incompatible liver transplantation with a preoperative rituximab. Transplantation 2012; 93: 99-105 [PMID: 22094955 DOI: 10.1097/TP.0b013e318239e8e4]

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.

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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.
  - **Multiple or large rituximab doses significantly increased the incidence of infection and early administration held no advantage** - *Egawa H, et al. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. Am J Transplant 2014; **14**: 102-114 [PMID: 24279828 DOI: 10.1111/ajt.12520]*
  - ?No role for addition of basiliximab.

Silke Rummler, et al. Current techniques for AB0-incompatible living donor liver transplantation. World J Transplant 2016 September 24; 6(3): 548-555

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.

M. Arias, M. López-Hoyos. ABO-incompatible living-donor kidney transplantation Nefrologia 2010;30(1):10-4.

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 accomodation.

M. Arias, M. López-Hoyos. ABO-incompatible living-donor kidney transplantation Nefrologia 2010;30(1):10-4.

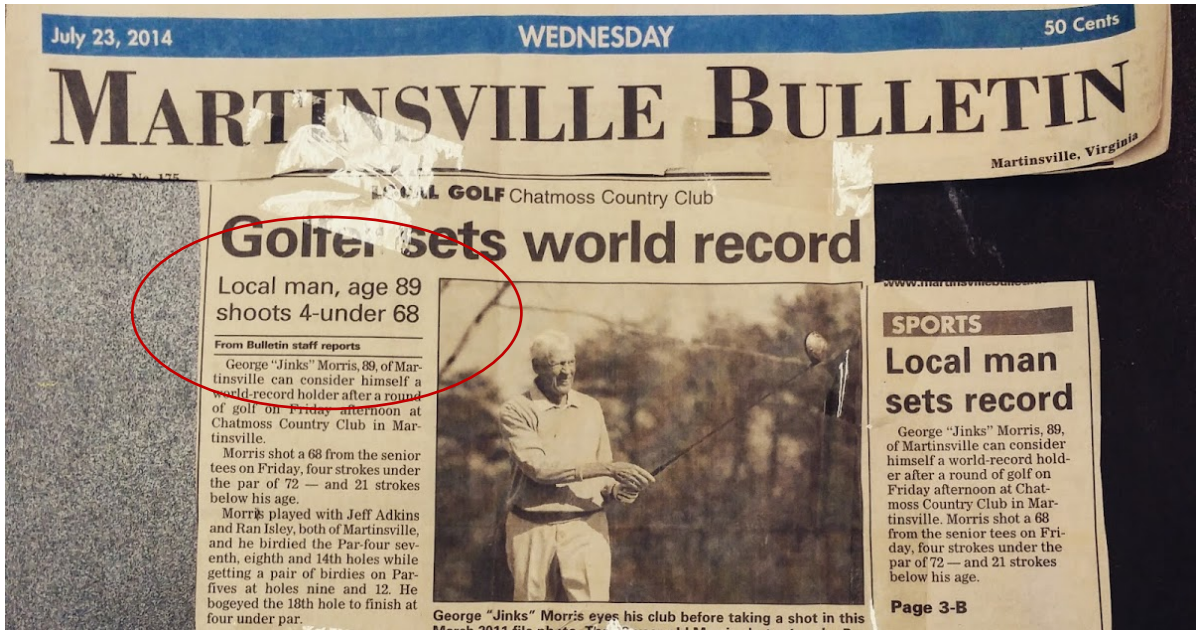
Accommodation

- 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.

M. Arias, M. López-Hoyos. ABO-incompatible living-donor kidney transplantation Nefrologia 2010;30(1):10-4.

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



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MARTINSVILLE BULLETIN

Martinsville, Virginia

GOLF Chatmoss Country Club

Golfer sets world record

Local man, age 89 shoots 4-under 68

From Bulletin staff reports

George "Jinks" Morris, 89, of Martinsville can consider himself a world-record holder after a round of golf on Friday afternoon at Chatmoss Country Club in Martinsville.

Morris shot a 68 from the senior tees on Friday, four strokes under the par of 72 — and 21 strokes below his age.

Morris played with Jeff Adkins and Ran Isley, both of Martinsville, and he birdied the Par-four seventh, eighth and 14th holes while getting a pair of birdies on Par-fives at holes nine and 12. He bogeyed the 18th hole to finish at four under par.

George "Jinks" Morris eyes his club before taking a shot in this

SPORTS

Local man sets record

George "Jinks" Morris, 89, of Martinsville can consider himself a world-record holder after a round of golf on Friday afternoon at Chatmoss Country Club in Martinsville. Morris shot a 68 from the senior tees on Friday, four strokes under the par of 72 — and 21 strokes below his age.

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