Mini-Review

ABO blood type incompatible lung transplantation

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Abstract: ABO-incompatible transplantation has been successfully performed in the kidney and liver. However, lungs are subject to strong rejection and are vulnerable to infection because they are directly exposed to air. Therefore, lung transplantation from organs with incompatible blood types has been considered a significant challenge. Due to the severe shortage of donors, ABO-incompatible lung transplantation might be a viable method to save critically ill patients with end-stage respiratory diseases. Herein, we review the worldwide published reports about both minor and major ABO-incompatible lung transplantations. In North America, major ABO-incompatible lung transplants have been performed in cases with clerical errors in blood typing. But they were successful with additional treatments following the protocol for ABO-incompatible transplants in other organs (multiple plasma exchanges and additional immunosuppressive therapy such as anti-thymocyte globulin administration). In Japan, major ABO-incompatible living-donor lobar lung transplantations have also been performed successfully when the recipient does not have an ABO antibody against the donor. This unique situation sometimes occurs when the recipient undergoes hematopoietic stem cell transplantation before lung transplantation, in which the recipient's blood type changes after hematopoietic stem cell transplantation. One infant and one adult had successful intentional major ABO-incompatible lung transplantation with both induction therapy and aggressive maintenance antibody-depletion therapy. Furthermore, an experimental antibody-depletion study has also been conducted to overcome ABO incompatibility. Even though intentional major ABO-incompatible lung transplantation has rarely been performed, several significant pieces of evidence have been accumulated to prepare for ABO-incompatible lung transplantation in selected cases. In the future, this challenge can potentially expand the donor organ pool and lead to improvements in the fairness of organ allocation.

Keywords: ABO blood type; ABO-incompatible; lung transplantation

Submitted Jan 11, 2023. Accepted for publication Apr 15, 2023. Published online May 15, 2023.
doi: 10.21037/jtd-23-48
View this article at: https://dx.doi.org/10.21037/jtd-23-48

Since lung transplantation was successfully performed in 1983 by the Toronto team (1), it has been established as one of the last options to save critically ill patients with end-stage respiratory diseases (2). However, there are still many challenges to be solved, and the chronic shortage of donor organs is one of the most significant among them (3,4). Effectively limited donor organ allocation using lung allocation scores and radical utilization of marginal donor lungs using ex vivo lung perfusion (EVLP) have been widely performed in the world to overcome the shortage of donor organs (2,5,6). According to OPTN/SRTR 2020 annual data report, the median waiting time for listed candidates in North America was shortened to be 1.4 months and waitlist mortality was 16.1 deaths per 100 waitlist years (7). By contrast, in Japan, where the shortage of donor organs is the severest in the world (the waiting time for cadaveric lung transplantation exceeds more than 900 days, resulting into an approximately 50%mortality rate), living-donor lobar lung transplantation (LDLLT) has been constantly performed in addition to the aggressive use of marginal donor lungs (8). However, its annual number remains between 10 and 20, making it difficult to solve the challenge

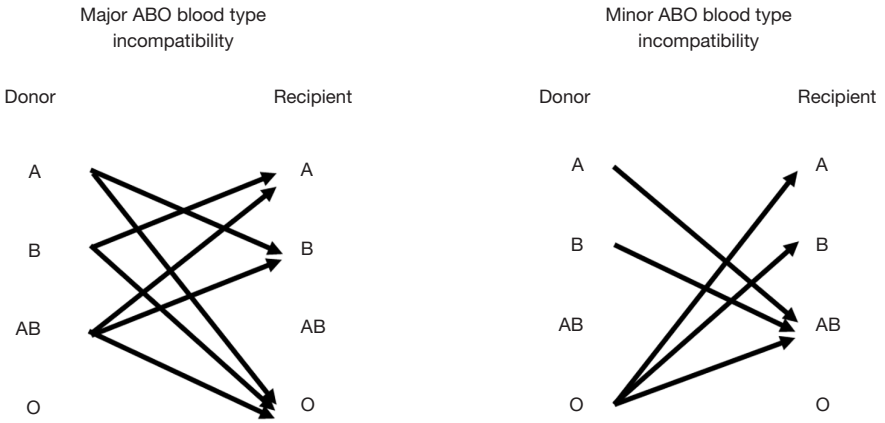

Figure 1 Major and minor ABO blood type incompatibility.

in the real world (9,10). Another viable option for expanding a donor pool is ABO-incompatible lung transplantation, as many ABO-incompatible kidney and liver transplants have been performed successfully. Therefore, in this mini-review, we reviewed ABO-incompatible lung transplantation as a viable option to overcome the shortage of donor organs.

In solid organ transplantation, many cases of ABO-incompatible organ transplantations, particularly kidney and liver transplantations, have been performed. In major ABO-incompatible kidney transplantation, Japanese groups reported excellent patient and graft survival using regimens consisting of plasmapheresis, immunosuppression, immunoadsorption, and splenectomy (11,12). They also showed similar outcomes to those of ABO-compatible kidney transplantation. In comparison, only two cases of intentional major ABO-incompatible lung transplantation in cadaveric lung transplantation have been reported worldwide (13,14). However, it is notable that 42 instances (0.4%) of accidental major ABO-incompatible lung transplantation were reported among 9,804 primary lung transplants, according to the database of the Organ Procurement and Transplant Network in the United States (15).

ABO incompatibility consists of major and minor incompatibilities (*Figure 1*). A major ABO incompatibility exists when a novel immunodominant sugar moiety (A: N-acetylgalactosamine; B: galactose) from a donor lung is transplanted into a recipient with the corresponding blood type antibodies (anti-A, anti-B, and anti-A, B). This clinical scenario occurs most frequently in blood type O patients who are receiving lung transplantations from blood type A, B, or AB donors. By contrast, minor ABO incompatibility most frequently occurs when a blood type O donor lung is transplanted into blood type A, B, or AB recipients. In a strict sense, ABO incompatibility means major ABO incompatibility in transplantation. In this review, we mainly focus on major ABO incompatibility because it is a clinical challenge, although minor ABO incompatibility is also documented. In cases of minor ABO incompatibility, it is known that the graft produces ABO antibodies against the recipient's red blood cells after a transplant of a solid organ that is minorly ABO-incompatible (16). The clinical phenomenon of autoimmune hemolysis caused by the adoptive transfer of viable lymphocytes from the donor during hematopoietic stem cell or solid organ transplantation is known as "passenger lymphocyte syndrome" (17). The incidence of antibody detection and hemolysis is reportedly low, intermediate, and high in kidney, liver, and heart-lung transplantations, respectively (16). Magrin *et al.* reported the first case after lung-only transplantation, showing that the possibility of developing ABO-incompatible hemolysis is higher in heart-lung or liver transplantation than in lung-only transplantation because its possibility depends on the mass of lymphoid tissues present in the graft (18). Even lung transplantation has been performed in cases of minor ABO incompatibility worldwide; however, complications have been reported (19-21). Salerno *et al.* reported that donor ABO antibody-derived hemolysis was developed in two out of four cases with minor ABO-incompatible lung transplants (19). Sano *et al.* reported the cases of thirteen patients with minor ABO-incompatible LDLLT, of whom five developed anti-A or anti-B antibodies in the serum and only one exhibited hemolytic anemia (20). Ohsumi *et al.* reported that two out of eleven patients with minor ABO-incompatible LDLLT developed anti-B antibodies in

Table 1 Major ABO-incompatible lung transplantation

Study	Publication year	Number of patients	Intentional or not	Age	Original disease	Living or cadaveric	Surgical procedures	Outcome
Pierson (15)	2006	4	No	Various	Various	Cadaveric	Various	Two alive with >3 years and the other 2 with poor outcome
Pierson (15)	2006	42	No	Various	Various	Cadaveric	Various	12% of patients with early death (<60 days)
Struber (13)	2008	1	Yes	21 years	Cystic fibrosis	Cadaveric	Bilateral	Alive and well for 265 days
Graseman (14)	2012	1	Yes	32 days	Surfactant protein B deficiency	Cadaveric	Bilateral	Alive and well for 6 months
Snell (22)	2013	1	No	17 years	Pulmonary fibrosis	Cadaveric	Bilateral	Alive for 9 years and died
Noguchi (23)	2022	5	Yes	Various	Pulmonary complication after HSCT	Living	Various	Alive and well
Akabayashi (24)	2022	1	Yes	11–19 years	Obstructive bronchiolitis	Living	Bilateral lobar	Alive and well

HSCT, hematopoietic stem cell transplantation.

the serum, and both showed hemolytic anemia (21). The frequency of passenger lymphocyte syndrome appears to be related to the volume of transplanted lymphoid tissue, and approximately 10^6 to 10^7 B lymphocytes would be sufficient to produce detectable levels of ABO antibodies in the organ recipients (18). Typically, antibodies appear approximately one week post-transplantation and are present for approximately one month. So, lung transplantation between patients with minor ABO incompatibility can cause the transient appearance of weak *de novo* anti-A and B antibodies. Because this occurs infrequently, this procedure can be considered a safe treatment in general.

Major ABO-incompatible lung transplantation is generally avoided because the recipient's anti-A or anti-B antibodies would interact with the corresponding antigens in the donor's lung capillary epithelia, resulting in acute or hyperacute antibody-mediated rejection. Most cases of major ABO incompatibility in lung transplantation in the world were discovered post-transplantation, and there are only a few reports of intentional transplantation (*Table 1*). Clerical errors in blood typing were found to be the cause in the cases that were discovered post-transplantation, and as of 2006, there were four case reports, with two cases of early death and two cases of long-term survival (15). In that report, an additional 41 cases were identified from 1992 to 2003 in the database of the Organ Procurement and Transplant Network in the United States, with five (12%) having an early death within 60 days post-transplantation (two cases died of primary graft dysfunction), comparable to ABO blood type-matched or mismatched cases from the same period (15). Even though these results are good, the British Transplantation Society's most recent guidelines state that they do not have sufficient data to make a recommendation (25).

In several cases in which major ABO incompatibility was found post-transplantation, the details were reported (22,26-28). Antibody titers of anti-ABO blood type antibodies were measured regularly immediately after the finding, and treatment followed the protocol for ABO-incompatible transplants in other organs (multiple plasma exchanges and additional immunosuppressive therapy such as anti-thymocyte globulin administration). Cases of stable graft function over the medium- to long-term, such as six or nine years after surgery, were also reported (22,29). On the other hand, there are few reports of intentional cases, with only two reported worldwide in the literature by 2022 (13,14). One was a lung transplant from a blood type AB cardiac arrest donor for a patient with blood type O cystic fibrosis (13). The patient underwent intensive pre-, intra-, and postoperative treatment to eliminate anti-ABO blood type antibodies, with periodic checks of antibody titers. The patient was confirmed to be alive and well nine months post-transplantation. The patient received a plasma exchange and rituximab preoperatively. Rituximab

was repeated and seven plasma exchanges were performed during the first week post-transplantation; however, due to elevated anti-A and B antibodies, rituximab was repeated and immunoadsorption therapy was performed five times beginning in the second week, after which both anti-A and B antibody titers remained below eightfold. In the other case, a lung transplant from a cardiac arrest donor was performed on a 32-day-old patient with surfactant protein B deficiency who was a blood type A recipient from a blood type B donor (14). In this case, except for preoperative plasma exchange, the patient was managed under the same level of immunosuppression as in a normal lung transplant, and periodic checks of antibody titers for anti-ABO blood type antibodies were performed according to the protocol for blood type incompatibility-related heart transplant complications, but the patient did not present any blood type incompatibility-related complications. At six months post-transplantation, the recipient's anti-B antibodies were negative.

In Japan, it is of interest that major ABO-incompatible lung transplantation has been intentionally performed in selected cases (23,30). In detail, ABO blood types can change after hematopoietic stem cell transplantation (HSCT), and some patients may not have the corresponding anti-A or anti-B antibodies in their resulting blood types. In this case, rejection may not happen even in major ABO-incompatible lung transplants if the recipient does not have antibodies against the donor's blood antigens. Therefore, in Japan, several transplant centers permit major ABO-incompatible lung transplantation in cases in which the recipient has no antibodies against the donor's blood antigens. ABO incompatibilities can occur after HSCT. In the reported samples, nine out of 31 patients had mismatched anti-A or anti-B antibodies and ABO blood type after HSCT (23). In these patients, the results of detecting blood antigens with forward typing were inconsistent with the results of detecting serum anti-A or anti-B antibodies with reverse typing. Actually, in five of the 31 patients with lung transplantation for lung injury after HSCT, the ABO blood type combination resulted in blood type incompatible transplantation; all five were LDLLT cases in which the relevant anti-ABO blood type antibodies were not present in the recipient and the usual immunosuppressive protocol was followed, but none of the patients presented with blood type-related rejection (23). Furthermore, there was no significant difference in post-lung transplantation forced expiratory volume in one second in the first year between patients who underwent ABO-compatible and incompatible lung transplantations. It should be considered that patients may develop immunotolerance after HSCT, which can lead to the non-production of anti-A or anti-B antibodies. Even though longer observation periods are needed to confirm the long-term safety of major ABO-incompatible lung transplantation even in these selected patients, these findings indicate that ABO-incompatible lung transplantation can be considered a viable option for expanding the donor pool for such patients. Based on this experience, most recently, Kyoto University Hospital announced that they performed a successful major ABO-incompatible LDLLT for a recipient who had an ABO blood type antibody against the donor's blood antigen (24). In detail, a right lower lobe from a father with blood type B and a left lower lobe from a mother with blood type O were successfully transplanted into their daughter with blood type O. In this case, rituximab was administered three weeks before transplantation, and plasmapheresis was performed in addition to the standard immunosuppressive regimen.

Unlike kidneys and livers, lungs are subject to strong rejection and are vulnerable to infection because they are directly exposed to air. As a result, lung transplantation from organs with incompatible blood types has been regarded as a significant challenge; however, as demonstrated in this review, numerous pioneering experiences with ABO-incompatible lung transplantation have been accumulated. Moreover, there are more experiences and knowledge available for ABO-incompatible lung transplantation. For example, there are two main phenotypes of blood type A, the A1 and A2, which differ in antigenicity as determined by the amount of surface antigens (31,32). The surface of a subgroup A1 erythrocyte reportedly carries approximately one million blood type antigens, while a subgroup A2 erythrocyte displays less than one-third of that number (33), which suggests the possibility of transplanting a blood type A2 donor lung into a blood type O or B recipient. In heart transplantation, infant ABO-incompatible transplantation has been considered routine in some centers with excellent early and long-term results, which might be due to the immature immune system in these small children (14). This fact also suggests the possibility of starting ABO-incompatible lung transplantation with infant and pediatric recipients. In the first intentional LDLLT at Kyoto University, the recipient was a pre-teen/teen age child and she received a single lobe from an ABO-incompatible donor and another lobe from an ABO identical donor, which might affect the outcome (24). Furthermore, Wang *et al.* reported an experimental antibody-depletion study to overcome

ABO incompatibility (31). The study showed that EVLP of the lungs with enzyme-containing perfusate removed over 97% of endothelial A antigen within four hours without any treatment-related acute lung toxicity. They also simulated an ABO-incompatible lung transplant with an *ex vivo* model of antibody-mediated rejection using plasma of the blood type O as the surrogate for the recipient's circulation using three donor lungs. Their findings eventually supported the notion that EVLP treatment can be used to deplete donor lung A antigen.

In conclusion, major ABO-incompatible lung transplantation has been avoided because of the nature of the lungs, in addition to acute or hyperacute rejection. Although intentional major ABO-incompatible lung transplantation has scarcely been performed, several significant pieces of evidence have been accumulated to prepare for ABO-incompatible lung transplantation. In the future, this challenge can potentially expand the donor organ pool and lead to improvements in the fairness of organ allocation.

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-48/prf

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-48/coif). TFCY serves as an unpaid editorial board member of *Journal of Thoracic Disease* from April 2022 to March 2024. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chen-Yoshikawa TF. ABO blood type incompatible lung transplantation. J Thorac Dis 2023;15(6):3437-3442. doi: 10.21037/jtd-23-48