

ABO-incompatible Organs a Viable and Necessary Source for Transplants

A Review of Current Models and Call to Action

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Abstract

Despite the astounding technological advancements of modern society, failure to receive a timely organ transplant accounts for the death of approximately 18 U.S. citizens each day. As the population continues to expand, so does the shortage of donor-recipient matching organs. In order to alleviate this deficit, medical researchers have addressed the most common barrier that accounts for donor-recipient denial: blood typing. Within recent years, immunological understanding has progressed leading researchers to believe ABO-incompatible organs may be a viable source for transplantation with unparalleled potential to expand donor availability. It is the intent of this review to increase public awareness of organ transplant issues, leading to, perhaps a global reorganization and revision of the organ transplantation system.

ABO-incompatible Organs a Viable and Necessary Source for Transplants

Ever since the first successful human organ transplant in 1950, worlds of mortal men have dared to hope that even death might be staved off in the face of physical degeneration. In the United States alone, there are currently 120,756 candidates awaiting a life-saving organ transplant. Of this population, a mere 24% will receive a transplant within a year of becoming waitlisted (“Organ Procurement,” 2013). Due to the complexity of the process, requirements such as size, proximity, human leukocyte antigens (HLAs), serologies, and blood typing quickly and effectively limit donations to a given recipient. Of these requirements, blood typing has often been regarded as the primary restriction factor as up to 30% of transplants are prevented based solely on ABO incompatibility (ABOi) (Genberg, Kumlien, Wennberg, & Tydén, 2010). In fact, to be considered a legal Organ Procurement Organization in the United States the institution must adhere to strict member policies. Such policies include providing proof of ABO blood typing on two separate occasions prior to adding the candidate to the waitlist (“Organ Procurement,” 2013). Despite its required position in the organ donation process, researchers have recognized the removal of this barrier would greatly expand donation availability and to decrease waiting list mortality (Irving, Gennery, & Kirk, 2012). Because of this, a great effort has been dedicated to the development of effective ABOi protocols pertaining to kidney (Takahashi & Saito, 2013), liver (Mendes et al., 2013; Song et al., 2013), and cardiac transplants (Urschel et al., 2013). Due to significant increases in immunological and pharmacological understanding, ABOi organ transplants may no longer be considered ineffective and instead embraced as practical, efficient, and beneficial to the transplant community.

Historical Overview

Similar to ABO-compatible (ABOc) organ transplants, ABOi transplant research has been focused on pre- and post-operative immunosuppression in order to remove, and maintain low levels of potentially reactive antibodies. Ever since the 1901 discovery of ABO blood groups by Karl Landsteiner, it has been assumed that all ABOi transplants would result in immediate hyperacute rejection (defined as rejection within 24 hours) followed by the death of the foreign graft. Studies have shown that the highest risk experienced by recipients occurs in the immediately following organ transplant validating such assumptions and attention to precautionary treatments (Montgomery et al., 2012). It was not until June of 1982 that Guy P.J. Alexandre dared to break from commonly accepted medical practices to propose and conduct the first ABOi kidney transplant (Alexandre et al., 1985). Modern transplant protocols practiced under dire circumstances include significant emphasis on preemptive treatment, consisting of lengthy plasmapheresis, and invasive splenectomies (Lipshutz et al., 2011). Previously utilized treatments involving splenectomies and repeated plasmapheresis are considered high risk as many complications have been observed leading to graft rejection and ultimately death. Newly proposed protocols strive to reduce graft rejection, patient mortality, and immunosuppressive related complications while enhancing the overall functionality, longevity, and assimilation of the ABOi transplanted organ.

Immunology may be considered a relatively recent field of study with key elements such as clonal selection being hypothesized just 50 years ago in 1957. This slow progression of development and understanding has allowed for the generation of erroneous ideas pertaining to tissue compatibility. In order to understand the true

controversy of ABOi organ transplants, it is first necessary to explore the immunologic concerns scholars now have based on outdated theories and procedures.

Immunologists now believe that all cells have surface markers in the form of intermembrane or peripheral carbohydrates and proteins that causes distinctions between cell types. This form of local cell to cell communication requires that direct contact be made between cells in order for recognition to be made. This contact is made between the antigen or ligand of one cell and the antibody or receptor of another cell. When a given antigen is a conformational match to a specific antibody, the two surface proteins will bond together through a variety of non-covalent bonds such as hydrogen bonding and Van der Waals forces. Receptor-ligand binding causes an internal conformational change within the receptor cell resulting in signal transduction and a cellular response.

Specific to this incompatibility concept are the blood typing antigens A and B that are known to be found on human erythrocytes. While type O individuals present no blood type surface antigens with which to react, type A and B individuals respectively present A and B antigens. Individuals that produce cells that express type A antigens also produce anti-B antibodies while those that produce type B antigen expressing cells conversely produce anti-A antibodies. Similarly, individuals that produce blood type O cells that express neither type A nor type B antigens also produce both anti-A and anti-B antibodies. Mixing type A antigens and anti-A antibodies will elicit an immunologic response causing the destruction of identified foreign red blood cells. Understandably, this has prevented the advancement of trials as graft assimilation is the primary intention of organ transplants.

But perhaps it is this mainstream awareness from which a prominent misunderstanding stems: ABO blood group antigens are not the sole causes of incompatibility. While it is undisputed that any transplanted organ cannot be completely cleansed of donor blood due to the intricate and delicate nature of blood vessel integration, this contamination causes very little post-surgery inflammation and complication. Instead, the proposed primary cause for hyperacute and acute antibody-mediated rejection is an interaction between donor organ ABO *histo*-group antigens and plasma circulating recipient blood type antibodies. Instead of leukocyte mediated inflammation and cellular degradation occurring primarily in the circulatory system due to blood contamination (which at low contaminant levels is unlikely to cause a dangerous systemic reaction), ABO *histo*-group antigens located on donor endothelial are likely to react and cause severe degradation of the donated organ. If necrosis is not stopped through a combination of immunosuppressive drugs, the organ will be rejected and cease to support the body in normal healthy function.

Ultimately, this knowledge leads researchers to only two possible solutions to achieve ABOi transplant success. Solution one involves the targeting of the recipient's antibody producing cells such that a reduced (complete or partial) number of reactive antibodies are produced to react with the foreign tissue. A second and much less explored solution involves altering the expression of ABO *histo*-group antigens presented on donor organ cells.

Modern and Yet Outdated Protocols: A Call for Change

In the mid-1980s a group of Belgian medical researchers began to investigate conditioned ABOi renal transplants using a complex and multi-redundant system

(Alexandre et al., 1985; Alexandre et al., 1987). This protocol included the removal of the spleen, continual plasmapheresis, A/B trisaccharide intravenous administration, platelet transfusion, antilymphocyte globulin treatment and triple immunosuppression maintenance comprising of corticosteroids, azathioprine, and cyclosporine. This initial protocol yielded a 75% graft survival within the first year as compared to a 4% graft survival in non-conditioned ABOi transplants (Cook, Graver, & Terasaki, 1987). As technology advanced, the system began to simplify with Japanese doctors leading the world in high levels of grafting success (Tanabe et al., 1996). While protocols vary depending on the medical center, the common foundation of each system involves the removal of recipient antibodies (specifically anti-A and/or anti-B antibodies) and limiting the rebound in antibody circulation following the transplant. Modern protocols can be separated into two components: desensitization and immune modulation.

Desensitization involves the removal of native antibodies and the reduction of circulating complement proteins that are heavily involved in foreign tissue degradation causing cell lysis. While anti-A/B antibody removal is important in ABOi grafts as a reaction is certain, complement involvement is currently an area of investigation. Previously associated with hyperacute rejection, studies have shown that complement recognition of foreign tissue is heightened in deceased donor grafts as the tissue has undergone stresses involved in death (Wasowska, Lee, Halushka, & Baldwin Iii, 2007). This indicates complement removal may be more helpful with deceased donor transplants. However, desensitization is performed using multiple plasmapheresis treatments 1-2 weeks prior to the surgical organ exchange. This limits ABOi transplants nearly exclusively to live donors thus questioning the need for complement removal. In

addition to a potentially unnecessary complement removal, plasmapheresis has been shown to be associated with a number of complications including coagulopathy and transfusion reactions (Chirnside, Urbaniak, Prowse, & Keller, 1981; McLeod et al., 1999). Plasmapheresis has been noted as a lengthy, non-specific, and potentially dangerous process when utilized in such an intense manner that is required for transplantation preparation. It is not necessary to remove all contents of a recipient's plasma and by creating a more specific system in which only necessary components are sequestered, it is possible to avoid such complications. After years of study and observation, the medical community is certain that a better designed system must be developed in order to more properly treat ABOi transplant patients.

The next phase involved in the complicated network of immunosuppression techniques is that of immune modulation. While desensitization is meant to remove potentially reactive components of the immune system, immune modulation is meant to prevent the further production of native antibodies and can be divided into two primary treatments: splenectomy and triple immunosuppression therapy. The surgical excision of the spleen is perhaps the most invasive and needless component of modern models. As a secondary lymphoid organ and an important blood reservoir in times of trauma, the spleen filters the blood removing old red blood cells and sequesters immune response causing antigens that may be circulating in the blood. Nearly a fourth of the body's lymphocytes are stored in the spleen and removal drastically increases a person's susceptibility to infection (Moynihan, 2013; Wasserstrom, Bussel, Lim, & Cunningham-Rundles, 2008). Intended as a final security measure in a redundant system, the removal

of the spleen is designed to reduce the native B-cell population and thus prevent the production of antibodies (Genberg et al., 2010).

The second component of immune modulation is triple immunosuppressive maintenance in which immunosuppression is used consisting of corticosteroids, azathioprine, and cyclosporine (Genberg et al., 2010). Each drug individually can be very damaging to the body and prevent normal functioning processes when used in high doses. It is for this reason that multiple are used in unison such that low doses may be used, providing the individual with effective immunosuppression without completely inhibiting processes needed for healthy functioning. As such, this cocktail of immunosuppressive compounds is an integral component of the remainder of a transplant recipient's life. It is due to this prolonged dosage that researchers are now indicating as the cause of a number of associated diseases. In particular, repeated doses of cyclosporine have been associated with neuropathy (Serkova, Christians & Benet, 2004) and nephropathy (Gheith et al., 2008) while use of azathioprine is now seen to correlate with hematotoxicity and hepatotoxicity (Schwab et al., 2002).

As is true of most medications, the mechanism of action of cyclosporine is complicated and involves multiple levels of cellular modification. Derived from the fungus *Tolypocladium inflatum gams*, this lipophilic cyclic peptide diffuses through the cellular membrane and binds to a cytosolic receptor known as cyclophilin. Together, the cyclosporine-cyclophilin complex binds to the protein phosphatase calcineurin. This causes a conformational change in the calcineurin which inhibits its serine-threonine phosphatase activity, thus halting downstream effects. Without cyclosporine, a proper immune response is mounted beginning with the increase in cytosolic calcium. High

levels of free cytosolic calcium indicate cellular stress and induce apoptosis through a number of pathways. In the most relevant pathway, calcium then binds and activates calmodulin (also known as calcium-modulated protein) which then stimulates calcineurin. Calcineurin then initiates the translocation of NFAT (nuclear factor of activated T cells) transcription factors from cytosol to the nucleus of T cells. A number of genes are then activated and interleukins are produced, advancing the immune response (Serkova, Christians & Benet, 2004).

Azathioprine differs in mechanism of action as it acts as an inhibitor of de novo pyrimidine synthesis. Once consumed, the azathioprine is converted to 6-mercaptopurine which then actively inhibits pyrimidine synthesis which are necessary building blocks for DNA. Ultimately this prevents cellular metabolism, particularly in immune cells, and all cellular functions thus lessening immune responses. Similar to cyclosporine and other compounds, azathioprine affects the body through more than one pathway and it is these previously uninvestigated divergences that cause serious health concerns. In order to provide patients with a better quality of life post-surgery, the new proposal of further scrutinized immunosuppressive drugs is necessary.

Due to less than satisfactory graft assimilation and survival rates, ABOi transplants under recent protocols have been used only under extreme and dire circumstances. However, with the notable potential of greatly expanding donor availability and saving lives just within the realm of current technology, researchers have been greatly motivated to design effective and functional systems.

Innovative New Protocols and Research

Isoagglutinin Adsorption in ABO-incompatible Transplantation

One such study, from Sweden, illustrates the observable longevity of kidney function after ABOi transplantation. The developed protocol involves a single dose of anti- CD20 antibody (commonly known as rituximab), administration of intravenous immunoglobulin alongside triple immunosuppression therapy, and immunoadsorption techniques (Genberg et al., 2010). Immunoadsorption is performed using newly marketed Glycosorb[®] ABO columns in place of less specific plasmapheresis (Valli et al., 2009).

The use of rituximab (375 mg/m^2 body –surface area) replaces the need for a splenectomy, a B-cell reducing therapy, as the CD20 marker is found exclusively on these target cells (Atzeni, Doria, Maurizio, & Sarzi-Puttini, 2007). Upon binding to the B-cell, the anti-CD20 antibody induces apoptosis through a combination of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity (Binder, Otto, Mertelsmann, Veelken, & Trepel, 2006). The depletion of B-cells is necessary to reduce the production of reactive antibodies that are responsible for mounting an immune response against the implanted foreign tissue.

The triple immunosuppressive therapy selected for in this program involves newer compounds that have not yet been seen to have associated complications: tacrolimus, mycophenolate mofetil, and corticosteroids. Tacrolimus acts to prevent the activation of T-cells and production of IL-2 (an inflammation inducing cytokine) through the dephosphorylation of the transcription factors. The dephosphorylation of transcription factors ultimately leads to the end of T-cell activation and consequently the prevention of IL-2 production (Brazelton & Randall E, 1996). Mycophenolate mofetil acts as an inosine

monophosphate dehydrogenase inhibitor that effectively halts the growth of T and B-cells (Brazelton & Randall E, 1996).

Finally, the use of corticosteroids is meant to limit or prevent large scale inflammatory responses. While symptomatically categorized by redness, heat, swelling, and pain, inflammation is the body's generalized response to foreign threats. The purpose of inflammation is to localize and remove both foreign agents and damaged tissue such that the body may begin to heal and function normally. The normal physiology of an inflammatory response begins with the activation of the enzyme phospholipase A during cellular injury (the result of transplantation and following immunologic sensitivity). Once activated, Phospholipase A breaks down membrane phospholipids into arachidonic acids which are further catabolized into eicosanoids such as prostaglandins, thromboxanes, leukotrienes, and lipoxins. Each contribute to the mechanisms of an immune response as thromboxanes allow for the transport of white blood cells (immune cells) and cytokines to the site of injury, thus initiating the process of inflammation. In order to prevent the damaging results of inflammation to a newly transplanted organ, corticosteroids are used to halt the process at the start of the cascade with inhibition of the phospholipase A enzyme. It was the detailed understanding of these compounds on human physiology that eventually led to clinical trials.

Fifteen ABOi kidney transplants utilizing the described protocol were then analyzed over the course of three years and compared against a control group of 30 ABOc kidney transplants completed under standard protocol. The functionality of the organs was then tested by assessing the filtration rate of the kidney's glomeruli. This data was quantified in terms of serum-creatinine concentrations. Normal serum-creatinine

concentrations in men are approximately 136 $\mu\text{mol/L}$ while women are slightly less with a concentration of 120 $\mu\text{mol/L}$ (Schillaci, Reboldi, & Verdecchia, 2001). The average serum-creatinine concentration over the first three years after ABOi kidney transplants in both men and women was found to be 127 $\mu\text{mol/L}$ while the average concentration for ABOc transplants was seen to be 133 $\mu\text{mol/L}$ (Genberg et al., 2010). Both values are considered healthy for kidney filtration rates thus indicating the new ABOi technique allows for excellent organ assimilation. In additional studies, donor endothelium tissue has been observed to, over time, express decreased quantities of blood-type antigens suggesting increased graft assimilation (Tanabe et al., 2011).

Implementation of a Protocol for ABO-Incompatible Kidney Transplantation: A Three Center Experience with 60 Consecutive Transplantations

With the initial pilot program instituted in Stockholm, Sweden yielding promising rates of both graft survival and functionality, Karolinska University researchers then attempted to expand facility utilization on an international scale. Approximately 20 European facilities accepted the protocol in Germany, Switzerland, Greece, France, Spain, the Netherlands, and the United Kingdom. Of these, three facilities in Uppsala and Stockholm, Sweden and Freiburg, Germany were selected and the results from 60 ABOi transplants were reported.

Between both compatible and incompatible blood type groups, the patient survival rate was 98% at 61 months. Interestingly, the donor graft survival in ABOi patients surpassed the ABOc graft survival rate of 95% with 97% of ABOi grafts surviving the first three years (Tyden et al., 2007). As previously stated, the highest risk

of rejection occurs directly after surgery indicating the long term effectiveness of ABOi transplants to be highly comparable to that of ABOc protocols (Montgomery et al., 2012).

ABO-incompatible Kidney Transplantation: A Japanese Review

At first mention of Japanese medicine, general population individuals might be inclined to relate the practice to the scientifically unfounded field of eastern traditional medicine; this could not be further from the truth. Ever since the first ABOi kidney transplant in January of 1989, Japan has pioneered the field of incompatible tissue grafting with protocols of the highest scientific caliber. Over the last two decades of transplant practice, Japanese researchers have not only developed numerous research teams dedicated to perfectionist improvements, but they have also made great efforts to educate the public and promote the regular use of ABOi organs (Takahashi & Saito, 2013).

As leading experts of ABOi transplants, the medical community in Japan has found great confidence in present and potential future protocols through a comparison of graft success through the decades. Within the first decade between the years of 1989-2000, nearly 451 ABOi kidneys were transplanted in Japan. These individuals had a *patient* survival rate of 92% within the first year, 89% within three years, 86% within five years, and 84% within nine years. These early *grafts* were found to have lower chances of survival with only 82% surviving the first year, 76% surviving three years, 70% surviving five years, and 58% surviving nine years (Takahashi & Saito, 2013).

Despite discouraging graft survival results, Japanese research continued in earnest and a decade of ABOi transplants later yielded significantly higher survival of both patients and grafts. Within the first year, 98% of patients (taken from a transplant

population of 1,427) survived the ABOi procedure, an 8% increase compared to the prior decade. Patient survival rates continued to increase with time as at three years 97% survival was observed (8% increase), 96% at five years (10% increase), and 91% at nine years (7% increase). As expected, graft survival followed the trend with 96% of grafts surviving the first year, a 14% increase over the prior decade. After three years, 93% of grafts were found to survive (17% increase) with 91% survival found at five years (21% increase). Finally, with the greatest increase, nine year transplants were found to have survived at a rate of 83% (25% increase) which places the treatment on a similar level with ABOc transplants (Takahashi & Saito, 2013). It should be noted that the differences found in graft versus patient survival rates are accounted for through the temporary use of dialysis before the implementation of a long term solution.

According to a summation of Japanese research, there are four main factors that have contributed to the significant increase in grafting results as well as the nationalized use of ABOi organs as a product of education. It was once previously assumed that ABO histo-group antigens were the reactive components of donor tissue that were responsible for hyper acute rejection. While some medical communities remain unconvinced, epidemiological evidence seems to indicate hyperacute rejection to be unrelated to these ABO histo-antigens (Takahashi, 2007). The rejection of this idea has led to a wider and more open-minded use of ABOi transplants by physicians.

A second factor thought to contribute to these successes is a further understanding of the underlying mechanisms of acute antibody mediated rejection. Researchers have separated this rejection into two categories which has allowed for increasingly specific targets for pharmacological therapeutic compounds. These

categories examine the specific causes of transplant rejection based on ABO-blood-group-related antigens and bacterial infections (Takahashi, 2007).

As suspected, such significant improvements in patient and graft survival would not be possible without protocol alterations or additives. As such, the third advancing factor—the use of novel immunosuppressants-- may be considered that of the most importance. Over the years, a specific cocktail of compounds has been cemented in the minds of health care providers as the golden standard of immunosuppressive therapy. However, recent research has indicated several of these commonly used drugs to have adverse long term effects. Without the proposed deviation from standard maintenance drugs, patients would continue to suffer long-term organ damage, a blatant contradiction to concept of tissue grafting.

The fourth factor leading to these medical advancements pertains less to science and more to the progression of communication. The formation of a systemized organization dedicated to the advancement and sharing of data has greatly decreased miscommunication and heightened the speed with which discoveries are made. This partnership of research facilities clearly defines the responsible and serious nature the Japanese medical community has taken in order to better the lives of their citizens. In addition to this astounding synergistic effort, this organization has also charged with the duty of educating the public such that ignorance does not bias transplant type selection and hinder the progression of acceptance (Takahashi & Saito, 2013).

Altering Surface Antigens of Donor Tissue

As previously discussed, in order for ABOi transplants to be effective, either recipient antibodies or donor antigens must be depressed. In 2007, an American based

company known as ZymeQuest announced its research that could revolutionize the concept of blood donation. According to a press release issued by the company, this company's technology aims to address the worldwide shortage of group O blood donations by altering the surface proteins of blood groups A, B, and AB. Though still under development, this technology uses naturally produced bacterial enzymes to degrade glycosylated protein antigens found on all but type O erythrocytes (Garratty, 2008). This would greatly reduce (but not entirely as Rhesus proteins do not illustrate susceptibility to degradation) the need to match blood types before transfusions.

If this technology were to come to fruition, it is conceivable that the same mechanisms could be used to eliminate the surface ABO histo-antigens on donor cells thus eliminating any risk of rejection by the host.

Decrease in ABO Antigen Expression Following ABO-I Renal Transplant

As established in previous literature, foreign tissue rejection is consistently seen to occur quickly after transplantation. High percentages of tissues that do not undergo hyperacute rejection (24 hours) have been known to last over a decade without complications highlighting the thought that perhaps the body has its own mechanisms that aide in assimilation. To tests this, Japanese researchers used immunohistochemical assays to determine the relative antigen expression of donated tissue over the course of ten years. A control group of four ABOc kidney transplant patients were used to illustrate a normal lack of antigenicity divergence. Quantification of the immunohistochemical assays showed 99.8% retention of normal blood type surface antigens (Tanabe et al., 2011).

In comparison, the results from a group of six ABOi (both type A and type B) kidney transplant patients yielded dramatically decreased antigen expression. Three months after transplantation, foreign kidneys displayed 91.8% antigen expression with a significant drop to 85.8% within five years. Within the ten years of transplantation, transplanted tissue was found to exhibit 64.1% original expression and 57.6% expression after ten years (Tanabe et al., 2011).

While this undoubtedly signifies graft assimilation, it also represents underlying mechanisms in which the recipient's body is naturally removing foreign surface antigens and preventing replacement through down-regulation of the glycosylated proteins. An advancement of this study and exploration of the uncharted natural mechanisms could greatly benefit ABOi transplant protocols through a similarly modeled reduction of reactive antigens. With promising studies such as these, it is all but certain that the successful nature of ABOi transplants will continue to advance.

Immunologic Failure Avoided in 10 Consecutive ABO-I Liver Transplants

As the most commonly transplanted organ (likely due to its redundant nature), the kidney is the central subject of study in nearly all ABOi transplant research. However, trailing the kidney as a distant second, the liver has also become an area of ABOi transplant development. One particular study from Seoul, Korea followed the graft health of 10 consecutive ABOi liver transplant patients undergoing a procedure and drug regiment similar to the previously described Swedish model. Notable differences include the use of plasmapheresis instead of the Glycosorb-ABO System and cyclophosphamide was used as an immunosuppressant for one week before switching to mycophenolate mofetil.

It was found that 100% of graft survived at 3 months with 90% of graft survival observed at 2 years (Song et al., 2013). All post-surgery complications were attributed to infection, and fungal pneumonia. These distinctions are exceedingly important as they conclude that complications were not mediated by antigen recognizing immunologic mechanisms indicating, yet again, that blood typing transplant tissue to be unnecessary when attempting to prevent immunologic rejection.

Collective Pediatric Heart Transplantation Analysis

Following the kidney and liver as the third most frequently transplanted organ is the heart. Unlike previous studies, most research pertaining to ABOi cardiac replacements is relevant to only one age group: infants. At birth, the human immune system is underdeveloped and it is this logic that propelled the initial investigation into ABOi cardiac transplants in infants. In order to assess the progress and effectiveness of such transplants, 85 pediatric ABOi cardiac transplants occurring within the Pediatric Heart Transplant Study were reviewed against 417 similar ABOc transplants. At centers performing both ABOi and ABOc procedures, there was not a statistically significant difference in freedom from rejection. However, when the same facilities were compared, it was noted that ABOi transplants were prone to infection 23.5% of the time while ABOc transplants were more likely to acquire infectious complications at 37.9% (Henderson et al., 2012). Ultimately, it was determined that ABOi transplants in young children had equivalent 1-year survival rates and in many cases were just as successful long term as ABOc patients. Upon completion of this analysis, Henderson et al. comes to a bold conclusion: in light of modern technology, the current policy of United Network

for Organ Sharing that gives ABOc transplants priority over ABOi is unwarranted and in great need of reevaluation.

Immediate Implementation and Sustainability of ABOi Protocols

An evaluation of current research and organ donor organization protocols clearly defines the United States as a body reluctant to embrace the idea of ABOi transplants as a common place procedure. Based on the wide success of numerous international facilities, it appears as though such reluctance is a rebellion to change rather than a rejection of scientific findings. The issue is further magnified when considering the role of the private sector, an organism that survives only through profit and convenience. Pressure from investors may cause some to even balk at the monetary and temporal investments required to actualize such a radically perceived change. With these factors considered, there is no question that many would be doubtful of a smooth transition in national protocol execution. But what are the realistic logistics of such a change?

Language Barrier

As previously stated, most prominent research to date has been done abroad, specifically in Sweden and Japan. Often, this creates a linguistic barrier and the communication and sharing of knowledge is delayed. However, in an age where English is nearly universal, it appears that relevant studies have all been translated into Standard English with the clear description of protocol techniques and results. These studies and articles have been conducted in a manner equivalent to that of American research. As such, the ideas and concepts contained in each are easily reproducible in American hospitals.

Understanding the difficulty in establishing new medical procedures, Swedish doctors tested the protocols ease of transition by implementing their protocol in 20 European facilities. Many of these facilities were located in countries with native languages different from English or Swedish such as German, French, Spanish, and Dutch. After successful results were reported in each facility, researchers deemed the protocol implementable without difficulty (Tyden et al., 2007).

U.S. Food and Drug Administration Approval

As is commonly known, the United States government maintains a rigid control over numerous trades and products. In order for a medically based procedure or product to be implemented in mainstream medicine, government regulators such as the FDA must first ascertain that they are both safe and effective. This means before the thought of ABOi transplants as a national solution was ever entertained, clinical trials must first be accepted according to government regulations. In addition to the approval of compounds such as specific immunosuppressants, the FDA must also approve medical devices and equipment such as the Glycosorb-ABO System. The process of FDA approval can be both expensive and time consuming. However, due to the extensive current trials in a number of facilities (including older protocols utilized in the United States) as well as the established nature of the pharmacological compounds, investments would be estimated to be much lower than that of newly developed drugs.

Equipment Availability: Glycosorb-ABO System

Despite its foreign origin of development in Lund, Sweden, the immunoadsorbent column known commercially as the Glycosorb-ABO System, appears to be in wide circulation and use. Having been made available in 2001, the system has been used in

Sweden to facilitate better ABOi transplants, ultimately leading to other more commonplace functions. Noted international usage in Tunisia, Germany, Canada, India and the United States began in 2006 indicating the technology to be readily available outside its home nation of Sweden.

Immunosuppressive Compound Availability

In order for successful implementation, it would be ideal that the most effective immunosuppressants used in the new ABOi protocols (tacrolimus, mycophenolate mofetil, and corticosteroids) already have a strong industrial base. This would prevent strain of production as the mechanisms of manufacturing and distribution would already be established. Such is the case with the newly proposed immunosuppressants as each are used in a wide variety of human and animal afflictions. Therefore, it is hypothesized that the wide-scale implementation of new ABOi protocols would not be hindered at the level of immunosuppressive compound availability.

Rituximab Availability

Similar to immunosuppressant availability is the established nature of rituximab—the seemingly single most important component of ABOi protocols. Rituximab is currently used to treat a number of disorders including chronic lymphocytic leukemia, and adult rheumatoid arthritis. Unlike the ABOi protocol that calls for a single dose, individuals suffering from rheumatoid arthritis use rituximab as a daily treatment. This strongly suggests the additional rituximab need for the implementation of ABOi protocols to be very achievable by current industrial manufacturers with little to no inconveniences.

Implementation Conclusions

While few can argue the implementation of ABOi transplants to be a simple matter, even fewer can argue the national implementation of any new protocol to be uncomplicated and direct. The system and regulations set forth in the United States are intended to protect its citizens from unfounded trials. However, numerous international trials clearly define a success that is achievable here in the United States such that bureaucratic agendas and cost effectiveness should be overshadowed by the lives of patients and family members that could be bettered through the availability of ABOi organ transplants. While Darwinian logic may be contested in many aspects, it has never been more clear than times such as these that we have but few options: change or die. Without a global policy change resulting in the regular implementation of ABOi transplantations, thousands are sure to die annually waiting for an antigenic match that is sure to come too late.

General Population Response: An Echo of Policy Maker Mentality

As the data seems to indicate, the technology of the current decade has advanced in such a way that ABOi organ transplants are both viable and practical. Despite these advancements and public implementation in nations abroad, the United States continues to stand behind an outdated policy of ABOc priority. This unwillingness to embrace change in a timely manner has fostered the indoctrination of false, antiquated concepts.

In order to illustrate this conjecture, random samplings of 26 United States citizens were recruited to participate in a survey of personal ideology. Each participant was asked a series of questions with the aim of ultimately quantifying and analyzing the beliefs of the general public. Each participant was determined to have a basic education that did not exceed undergraduate level studies. The participants were then given the

same basic information regardless of their familiarity with organ transplants. “In the United States, 30% of organ donor denials are determined based on blood type incompatibility. New international studies examining up to three years after organ donation strongly suggest incompatible blood type denials to be needless as successful procedures have been developed to accommodate such transplants. Do you think United States organ donor organizations should change their policies and more readily accept blood type incompatible transplants?” When provided with this information, a 92% majority stated they believed a policy change to be in order. Despite indications of strong progressive attitudes, the conditioned, antique nature of the group was quickly revealed.

The participants were then given the following information: “Current data demonstrated in Sweden and Japan show that ABOi (blood type incompatible) transplants to be just as successful as ABOc (blood type compatible) transplants given the newly designed protocol.” Individuals were then asked to express their personal preference were they to need a transplant as ABOi, ABOc, or no preference. Given the previous response, it was expected that individuals would overwhelmingly express no preference. In reality, only 50% of participants indicated no preference while 42% specified a preference for ABOc.

These visibly conflicting results appear to demonstrate significant public resistance to defined beneficial change. While this is not only indicative of a lack of efforts to properly educate the public, it may also be considered a reflection on the mindset of those responsible for the maintenance of current organ sharing policies. Perhaps the real root of this issue pertains more to a resistance in change rather than a

rejection of the science. Such possibilities highlight the role of organization leaders and raise troubling questions of ethical responsibility.

Conclusions

In a sweeping assessment, data from numerous studies collectively support ABOi organ transplants protocols as both safe and effective with graft and patient survival rates often equal to or higher when compared with ABOc control groups (Genberg et al., 2010; Henderson et al., 2012). As such, these newly developed protocols may even be superior to current ABOc protocols due to the enhanced emphasis placed on anti-rejection methods. Despite the existence of such high quality protocols, ABOi transplants continue to be recommended in many facilities only for patients in dire need with no other matching ABOc donors (Hwang et al., 2013). Established data firmly indicates the viability of ABOi kidney (Genberg et al., 2010) and liver (Song et al., 2013) transplants with the adoption of proposed protocols and even suggests the possibility of more efficient ABOc procedures. However promising, more research and drug regiment development is necessary before the introduction of cardiac ABOi transplant into mainstream practice due to highly variable cardiac antigen expression (Gehrie, Cates, Nian, Olson, & Young, 2013). Overall, the practice of ABOi organ transplants has been neglected in the United States with East Asian countries like Japan leading the world in research and development. Currently, nearly 30% of live donor kidney transplants occurring in Japan are done using ABOi donor kidneys (Takahashi & Saito, 2013). This progressive thinking has allowed doctors to prolong and save the lives of many recipients who would not have found an ABOc donor match otherwise. It is for this reason that a review of these studies is essential for wider publication and recognition in hopes of

altering American transplant policies to ultimately expand donor availability and save lives.

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