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Review Article

The Anti-thymocyte Globulin use makes kidney transplantation journey smooth

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Abstract

Background: The most common immunosuppressant, Anti-thymocyte Globulin (ATGs) has been widely used by clinicians for the treatment and prevention of rejection at the time of organ transplant. Transplantation is the best option for the people with renal failure at end stage, requiring replacement of renal therapy. This is a promising treatment option with significant benefits in terms of mortality and morbidity. ATG prevents organ rejection by inhibition of activated T-cells and other immune and non-immune cells. The aim of the study was to compare different induction regimens with ATG for the survival of smooth kidney transplantation.

Methodology: Studies of the last 20 years, focusing on kidney transplantation and the efficacy of anti-thymocyte use for kidney transplantation were reviewed for the study literature. The keywords used were Kidney Transplantation, Induction agents, ATG, Allograft, Immunosuppressant Agents.

Results: Literature suggested that the most important problem with transplantation is the protection of the allograft from activated immunological forces, which begin to react early in the period after transplantation and cause significant damage with serious short-term and long-term consequences. This process is called rejection, which is usually classified as cell-mediated and antibody-mediated rejection. The phenomenon mediated by cells causes concern, as it is the cause of future failures and damage to the allograft. To combat these phenomena with different results, various strategies were adopted. Among these therapies, ATG has recognized the exceptional importance of preventing cellular mediated rejection, allowing allotransplants to function smoothly with the greatest possible long-term benefits.

Conclusion: It can be concluded on the basis of previous studies that ATG as an induction agent, is more efficient in reducing the rejection rate in the renal transplantation as compared with other agents.

Keywords

Kidney Transplantation, Induction Agents, Anti-thymocyte Globulin (ATG), Allograft, Immunosuppressant Agents.

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Introduction

The field of kidney transplantation has attracted scientists and physicians since the beginning of the late 19th century. Major advances in medical field has enabled the physicians to understand better the science of immunity, body`s defence mechanism and helped surgeons to perform a collaborative act of transplanting human organ from one to another individual with success despite having initial period of failure, major credit goes to the availability of the immune suppressant medications in the early era of the 1980s[1&2]. Knowledge of immune system activation and advent of immune-modulatory drugs has resulted in a winning outcome in terms of allograft and recipient survival which is promising factor in organ transplantation and this is the main area of research which has revolutionized kidney transplant as a definitive and successful treatment with the quality of life as other members of the society at the cost of some complications which are bearable and manageable[3&4].

This is reflected today by the increasing number of transplants with significant survival. One of the main factors of this success is the use of strong and powerful induction agents in the pre- and postoperative period, helping recipients to obtain an alien organ by suppressing their immunity and thereby influencing the fate of the renal graft[5]. The principle of induction therapy is using specialized drugs, usual antibodies along with conventional immunosuppressant to block the immune pathway[6&7]. At present, widely used induction agents are anti-thymocyte globulin (ATG), anti-receptor interleukin antibodies (alemtuzumab and basiliximab) and anti-CD-20 antibodies (rituximab), as well as other agents such as immunoglobulins[8&9]. Induction agents are antibodies which are capable of blocking the immune pathway at different points and result in suppression of host immune activation which is a major threat to the foreign allograft. Immunosuppression is a complex process and vital step to safeguard allograft and this achievement has resulted in widespread use of organ transplant around the world[10&11]. The most of the transplant units use various combinations of agents, as mentioned above, as induction immunosuppression all over the world with outstanding results[12].

Common induction agents used in renal transplant

ATG is a polyclonal antibody which has potential to counteract a variety of antigens located on T-cell surface including major histocompatibility complex derived from the immunized rabbits called thymoglobulin[13&14]. Atgam is another preparation derived from immunized horses but not in clinical use[15]. This agent is used as an induction drug and has a vital role in combating acute cellular region by regulating different pathways of rejection by depleting T cells thus reducing CD4/CD8 ratio, affecting complement pathway and inhibiting complement-mediated cell lysis and therefore halting deleterious consequences and also helps in increasing T regulatory cells which has favorable effect on long-term graft outcome[16].

Red cells are immune to its effect because anti-red cell antibodies have been removed while its formulation. Administration of thymoglobulin has recommendation through a central line with the use of pre-meds to avoid any allergic reaction with regular monitoring of white blood cells and platelets[17&18]. Alemtuzumab (Campath) is a monoclonal antibody which does not affect

the complement system. It targets CD-52 receptors on lymphocytes macrophages, monocytes, natural killer and some granulocyte. Primarily this agent had been used to treat leukemia, lymphoma, and multiple sclerosis[19-21]. Alemtuzumab has comparable efficacy with thymoglobulin in terms of allograft survival with the additional advantage of succeeding steroid-free regimen[22]. Pneumocystis jiroveci and cytomegalovirus prophylaxis are highly recommended for a minimum duration of six months. The drawback of using Alemtuzumab is delayed the appearance of antibody-mediated rejection as a consequence of late regeneration of B-cells[23&24].

Muromonab (OKT3) is the first monoclonal antibody used in humans. It is purely murine, but it is not using any more since the availability of thymoglobulin[25, 26]. Interleukin 2 receptor antagonists, Basiliximab, also used as an induction agent acts against CD-25 receptors on act T-cells resulting in their depletion. This drug is especially recommended in two conditions. First, in recipients with low risk of rejection and secondly where ATG use is not recommended or safe. It is well tolerated with the added advantage of no monitoring required[27-29]. Rituximab is an anti-CD-20 antibody, chimeric antibody. It active against B-cells which possess CD-20 receptors. It is an integral part of ABO blood grouping and Human Leucocyte Antigen (HLA) incompatible transplants and also has an important role in the management of post-transplant lymphoproliferative disorder[30]. It has a good safety profile and its use is equivalent to surgical splenectomy. Rituximab leads to cross match difficulties due to the generation of autoantibodies[31&32].

Immunoglobulin exerts its role as an immunomodulatory agent and halting complement activation which results in protection against complement-mediated injury [33&34]. It is used as a part of desensitization protocols pre-transplantation and for treating antibody-mediated[35&36]. Its use can manifest some side effects which could be nonspecific like body aches pains but it can lead to meningitis like the picture, anemia acute kidney injury. Unwanted effects can be avoided by hydrating the individuals and use of iso-osmolar solutions[37]. Different agents as mentioned above has the capacity to modulate the immune system. Many studies have shown the effectiveness of all these agents in the transplant recipients but no standardized practice has been established to date advocating superiority of one agent over the other thus every center has its own protocols based on their experience[38]. These agents are an integral part of transplant medications and often combination regimens are used to achieve success both short term and long term and these agents are mandatory to use when performing transplantation across the borders like HLA and ABO incompatible individuals[39].

ATG is the best choice for Renal Transplantation

It is a proven fact that antibody-based induction agents with conventional immunosuppressant have resulted in improved graft survival with fewer incidences of rejection episodes[40]. Choice of induction agents is usually based on the pre-transplant risk evaluation and anticipating events postoperatively based on the identified risks with the consideration that the selected induction agent will be potent enough to combat the anticipated

complications. Risk factors are HLA/ABO incompatibility, HLA mismatches, ischemia-reperfusion injury, live versus cadaveric transplant, hemodynamic shifts, infections and graft function[41]. Despite all these considerations Centre base preferences are there for the choice of agent. So the selection of an appropriate induction agent with the capability of addressing all the mentioned concerns will be very cost effective by reducing morbidity and mortality[27].

Many studies compared ATG with other induction agents, as mentioned above has concluded with the superiority of thymoglobulin[42]. Kidney Disease Improving Global Outcome (KDIGO) in 2009 has stated clearly to use ATG for the prevention and treatment of acute cell-mediated rejection[43]. This has been observed both retrospectively and prospectively that incidences of rejection are remarkably low with ATG induction associated with reduced post-transplant untoward events as well[44]. This is the result of lymphocyte depletion which suppresses inflammatory markers as well. Some studies proposed induction with basiliximab in low-risk individuals but later on it has been proved that the ATG induction regimen holds superiority over all other induction agents irrespective of the individual risk[45]. The most important and only factor which distinct ATG as an induction agent of choice amongst others is its capability to the remarkably reduced incidence of de novo donor-specific antibodies (DSA) which is a potent risk factor for antibody-mediated rejection[46]. Thymoglobulin use results in higher infection episodes but lesser Cytomegalovirus (CMV) incidences which is another benefit which persuades its use to be considered[47&48]. Administration of this drug preoperatively shortens hospitalization period with reduced the incidence of delayed graft function by blocking inflammatory mediators, chemokines, and cytokines so preventing ischemia-reperfusion injury which is the main mechanism for allograft injury leading to chronic allograft nephropathy[49-51]. Thymoglobulin superiority over horse anti-thymocyte globulin (hATG) has also been proved in terms of lesser rejection episodes with the ultimately lesser risk of delayed graft function as low as only 1% in a 10-year graft survival period[52]. Sustained lymphopenia and deactivation of inflammatory path pathway is the major impact of thymoglobulin use which is translated into smooth journey post-transplant due to far lesser events of delayed graft function and rejection episodes as compared to other agents used as a part of induction regimes[53&54]. Majority studies have reviewed the immunosuppressive effect of ATG and basiliximab and confirmed that the first agent has better and sustained impact on recipient immunity than later with better graft survival[55]. We suggest the use of basiliximab is to be limited to the conditions where ATG use is not suitable or recommended. Some centers in America are known to use Alemtuzumab. Few studies tried to compare it with rabbit anti-thymocyte globulin (rATG) especially in the population who received a simultaneous kidney and pancreas transplant, failed to draw major conclusions due to improper study designs and randomization and population but higher morbidity, mortality and graft loss was observed. Alemtuzumab and emergence of some autoimmune diseases. This effect has been attributed to memory T-cell[56]. ATG is the agent studied extensively due to its significant beneficial impact on the recipient and graft, to standardized its dose and establish a minimum dose benefit ratio in order to avoid untoward effects which could result due to higher dosages. Minimum effective total dose agreed upon based on different studies is 6mg/kg, the

range is 6-9mg/kg which can be divided into 4-6 doses. This drug has a potential to cause cytopenias resulting into serious infections and malignancies warrant its judicious use with close monitoring[16,57&58].

Randomized controlled trials and systematic reviews have concluded that Rituximab use is beneficial in ABO-incompatible transplants only not in HLA incompatible. Its use is associated with adverse cardiovascular outcomes[59]. Rituximab is not devoid of its cytopenic effect and morbidity and mortality issues related to the onset of serious infections long term. Enough data has supported the use of ATG and this practiced has been adopted globally with much confidence and improved outcomes and this review article also recommends the same practice to be continued until its use is precluded due to certain contraindications[27&60]. Thymoglobulin is a T-lymphocyte depleting agent. T-lymphocytes are the first line defense of the recipient towards a foreign allograft which is dampened by this drug, helping the host to accommodate graft. It is not only used as an induction agent but also for the treatment of acute cell-mediated rejection[61&62]. KIDIGO guidelines 2009 recommends ATG induction with triple immunosuppression either tacrolimus or cyclosporine-based, mycophenolate mofetil and prednisolone[63]. These drugs are recommended to be used in specialized centers, by the staff who are properly trained for administering these drugs and monitoring. ATG is cutting edge intervention used in solid organ transplant which creates the host environment to harbor allograft by conditioning the immunity with remarkable outcomes[64].

Anti-thymocyte Globulin Administration

Check hypersensitivity to the drug by subcutaneous or intradermal test dose. The recipient should be monitored very closely throughout its administration for any allergic or cardiac instability and one should be prepared to handle possible complication immediately[65]. Large or central veins to be used for the infusion to avoid flow issues and thrombophlebitis, though few European centers reported their uneventful experience through peripheral access[66]. Infuse it with an inline filter after the scheduled methylprednisolone. No other drug to be given through the shared connector except isotonic sodium chloride, if required[67]. If ATG and rituximab both are to be used then ATG should be preceded followed by Rituximab and these infusions should not be started without pre-medications. In case of hypersensitivity administer epinephrine 1:1000 subcutaneously, resuscitation as per needs, inform the authorities and documentation in the records so that this drug shouldn`t be administrated in future. Induction infusion should be started before establishing perfusion of the allograft.

Usually, six doses are recommended[68]. It is stated that the first three doses can be administered safely without affecting lymphocyte but remaining dosages to be planned according to white cell and platelet count[69]. The recipient should also receive Cytomegalovirus and Pneumocystis jiroveci pneumonia prophylaxis along with oral fluconazole. Drugs should adjust according to the estimated Glomerular Filtration Rate (GFR) and be revised periodically based on the deterioration or improvement of GFR[70&71]. The purpose of this article is to discuss the role of various immunosuppressant, with particular emphasis on the use of ATG as an induction agent chosen to protect allograft rejection during the post-transplant period, which is the most vulnerable to rejection in T-lymphocyte transplantation.

Conclusion

Based on the detailed literature review, it can be concluded that ATG as an induction agent, which is the main choice, has obvious superiority over other agents in terms of reducing the rejection rate, in the renal transplantation. This antibody inhibits the blockage of chemokine's and cytokines by their receptors, preventing damage to ischemia-reperfusion, which in earlier period causes adverse effects on the graft and prevents long-term graft function, which is a real success in terms of transplantation and survival.

Conflicts of Interest

None.

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