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Review Article

The Newest Medications in Kidney Transplantation and their Mechanisms of Action

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ABSTRACT

Purpose: In recent years, many new immunosuppressive drugs have been discovered and developed for clinical use in transplantation. This review focuses on new drugs and novel strategies that have been shown to have immunosuppressive activity in patients.

Materials and Methods: The literature was reviewed.

Results: The introduction of cyclosporine in the early 1980s improved renal allograft survival by approximately 15 percent at one year post transplant. However, cyclosporine failed to enhance long term graft survival. In addition, transplant recipients are at risk of significant side effects due to immunosuppression, including infection, cardiovascular disease, hypertension and malignancy. The limitations constitute the rational for the continued development of new immunosuppressive agents.

Conclusion: The therapeutic armamentarium for transplant immunosuppression continues to broaden and become more complex, as does the variety of potential drug combinations or protocols. Further studies in a large number of individuals is required to clarify the role of new immunosuppressive agents and novel strategies in transplant recipients.

KEY WORDS: new immunosuppressive agents, transplantation

HISTORY OF IMMUNOSUPPRESSIVE THERAPIES

The first immunosuppressive therapeutic method was initiated by applying a total body irradiation. Azathioprine was discovered at the beginning of 1960s. Treatment with Azathioprine together with Prednisolone was administered as an immunosuppressive protocol for many years. Polyclonal antithymns (ATG) and antilymphocyte antibodies (ALG) were introduced at the middle of 1970s. With Azathioprine and Prednisolone based protocols and by the use of ATG and ALG in treating steroid resistant rejections, success rate of kidney transplantation reached 50% during one year and mortality rate decreased to almost 10-20%.

A great revolution was made by the discovery of Cyclosporine from Toly Pocladium Inflatum fungus by which survival in kidney transplantation was increased to 80%. The decrease of corticosteroid usage and the improvement of medical

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services, considerably reduced mortality rate. The therapeutic protocol was changed to triple therapy with Cyclosporine, Prednisolone and Azathioprine. In spite of positive effects of Cyclosporine, its chronic and acute nephrotoxic effects were gradually manifested.

In 1985, OKT3 was introduced as the first monocolonal antibody and it was used in the treatment of first onset of rejection as well as in rejections resistant to steroid and as an induction therapy. At the beginning of 1990s, these treatment modalities led to the increase of one-year survival of transplant to 90% and to a considerable decrease of mortality.

Later progresses included the discovery of Tacrolimus and Mycophenolate Mofetile (MMF). Tacrolimus was initially used in liver transplantation and then in kidney transplantation as Cyclosporine substitute.

As a more effective drug, MMF was gradually used instead of Azathioprine. Daclizumab and Basiliximab, which are two newer monocolonal antibodies, have been administered in kidney transplantation in recent years. They proved to be effective in reducing the incidence of acute rejection and delaying it, as well as in treating acute rejection.

Sirolimus was added to immunosuppressive medications at the end of 1999, some other new medications which were also studied will be discussed later on.

1. Mycophenolate Mefetile (MMF or Cellcept®): This medication which is more effective than Imuran in preventing acute rejection in kidney recipients from cadaver was added to transplant medications in 1995 after some clinical studies.[1] Mycophenolic acid (MPA) is the active ingredient of this drug.

Mechanism of action: MMF is a reversible inhibitor of Inosinate Monophosphat Dehydrogenase (IMPDH) enzyme. This enzyme has a role in porine biosynthesis and is more effective than inosin in Guanosin Nucleotides production. The decrease of Guanosine Nucleotides has elective antiproliferative effects in lymphocytes.[2] In fact, this medication has specific antimetabolite effects. Contrary to calcinosin inhibitors (such as Cyclosporine and Tracrolimous) and Sirolimus, MMF has no impact on Cytokine production and in contrast with Azathioprine, it has no effect on lymphocytes and neutrophils. MMF reduces the adhesion of molecules to lymphocytes and consequently decreases their adhesion to the vessels' endothelial cells. It inhibits mononuclear cells migration to the rejection area by which it could be effective in treating the rejection episodes. It also prevents proliferative arteriolopathy by which it could prevent chronic rejection.[3]

The most important adverse effect of MMF is on gastrointestinal system, as it causes diarrhea in 30% of the cases. The decrease of dosage can often prevent diarrhea. It should not be used with antiacids and Cholestyramine.

2- Sirolimus: This medication is a macrolid antibiotic that is structurally similar to Tacrolimus. It was clinically introduced to the world of transplant in 1999 after a series of clinical studies.

Together with Cyclosporine and Prednisolone, it considerably reduces acute rejection incidence at the beginning of transplantation. It has the same immunosuppressive power of Cyclosporine, yet, more effective than MMF with more side effects.[4]

Mechanism of action: Sirolimus is linked to a protein (FK binding protein) in cytoplasm. This complex has an inhibitor effect on the Target of Rapamycine (TOR). The inhibition of TOR could reduce cytokine related cellular proliferation at G1 to S cellular division phases. Thus, this mechanism affects hematopoetic and non-hematopoetic cells.[5] Sirolimus together with Tacrolimus could form a much more effective regimen that could be administered with a lower dosage.

Sirolimus is metabolized in the liver by CYP3A and P-Glycoprotein. Its renal excretion is low, so that in case of renal function impairment there would be no need of reducing dosage; however, it should be adjusted in liver function impairment.

Like Cyclosporine, Sirolimus has interaction with calcium channel blockers, antifungal, anticonvulsive, and antituberculosis drugs. Its two important side effects are hyperlipidemia and thrombocytopenia. Patients with considerable preoperative hyperlipidemia are not good candidates to receive Sirolimus. In addition, its tubular toxic effect could lead to hypokalemia and hypomagnesemia.

3- Humanized Anti-TAC Monoclonal

Antibodies: These drugs include Basiliximab and Daclizumab, which act against alpha-chain of Interleukine 2 (TL2). This receptor only increases in activated T cells. Following its link with the antibody, the reaction caused by TL2 is blocked. These drugs complete the effect of calcinorin inhibitors, which reduce Intercolin-2 production, and their most important effect is to prevent acute rejection onset.

Murine monoclonal antibody is the origin of both drugs. Human IgG was substituted for 75% of the molecule in Basiliximab and for 90 % in Daclizumab.

Regarding that the immunogenisity of these medications is low and no considerable amount of antibodies is produced against them, their half-life would be higher (more than 7 days) and no first-dose reaction would be seen.[6]

NEW IMMUNOSUPPRESSIVE MEDICATIONS

New considerable medications have been produced. Little changes have been induced in some to decrease side effects and improve therapeutic index. Some others could cause significant changes in immunosuppressive therapies in near future, if clinically approved.

MODIFICATIONS OF AVAILABLE DRUGS

1. RAD: This drug is derived from Sirolimus and structurally similar to it, but with more oral absorption. RAD could be used together with Cyclosporine, while Sirolimus should be administered with an interval of 4 hours after Cyclosporine. Besides, RAD has a shorter half life than Sirolimus.[7]

2. ERL080A: This drug is enteric-coated type of Mycophenolate with lower gastrointestinal side effects and it could be administered with a lower dose.

3. FTY 720: It is a new immunosuppressive drug, which reduces B and T cells in the peripheral blood, while it increases them in lymph nodes and Peyer's Patch by affecting lymphocyte chemokine receptors. Thus, lymphocyte infiltration is inhibited in allograft and long lymphopenia is developed. FTY080A has no effect on the amount and function of granulocytes. It promotes immunosuppressive effect of Cyclosporine.

NEW MONOCLONAL ANTIBODIES

1- HuM291: This drug is a humanized OKT3. It is a human and hybrid provided by the transmission of complementary determining region of OKT3 to human IgG and mutation of single amino acids. This variant of OKT3 does not activate human T cells; however, it has strong immunosuppressive effects.[9] Regarding that the immunogenisity of this medication is much lower than OKT3, its half-life would be longer, approximately 142 hours.[10]

2- T10B9.1A: This murine monoclonal antibody reacts against an epitope located on T lymphocyte receptor (alpha/beta-heterodimer). Since it is not a mitogen, it does not have the complications caused by cytokine, which are seen by OKT3 use. Additionally, it accelerates the improvement of rejection episodes that lead to renal failure.[11]

Regarding murine origin of this drug, there is a high possibility of antibody formation against it; however, since there is a little interaction between T10B9.1A and OKT3, it could be used in patients who do not respond to OKT3.[12]

3- Anti-ICAM-1 antibody (Enlimomab): A considerable number of adhesion molecules take part in the interaction between T cells, antigen presenting cells, and target cells. Among these the reaction between leukocyte function associated molecules (LFA-1) in lymphocytes and intercellular adhesion molecule-1 in cells that provide antigen is of great importance.[13]

Primary experimental studies indicated that murine monocolonal antibodies which are produced against ICAM-1 could delay but not prevent acute rejection. A multicentral randomized placebo controlled study was conducted on 262 cadaver renal recipients. Enlimomab was administered in Enlimomab group for 6 days. This group was compared with placebo.[14] All patients received Cyclosporine, Azathioprine, and Prednisolone. No significant difference was observed between the two groups, regarding clinical purposes. Hence, the useful role of these antibodies is not definitely clear and further studies are needed to determine whether this role would be useful for just high risk groups or all groups.

4- Odulimomab: This antibody is formed

against alpha-chain of LFA-1. The effect of this antibody was compared with rabbit ATG in a multi-central study. Clinical tolerance for this medication was better than ATG, while rejection onsets at the first 10 days were more in Odulimomab group. However, the incidence and severity of acute rejection onsets at the first three months, survival of transplanted kidney at the first year, and the incidence and severity of infection in both groups were similar.[15]

5- Alemtuzumab (Campath-1H): This human monoclonal antibody is formed against CD52 of lymphocytes. It is a very effective drug by which patient would have a proper status with a low dose of Cyclosporine only as an immunosuppressive drug.

In a study, 31 cadaver recipient patients receive 20mg IV dose of this drug together with 500mg Methylprednisolone at the day of surgery, this dose was repeated on the following day. Afterwards, Cyclosporine was started 72 hours postoperatively. During 21 months follow-up 6 patients developed acute rejection episodes, which were treated by steroids and one patient, died of cardiac ischemia. Twenty seven out of 29 patients with normal renal function received only a low dose of Cyclosporine.[16]

6- OKT 4A: A murine monoclonal antibody is formed against CD4. It inhibits co-stimulatory function of CD4 molecule. The decrease of rejection incidence and low toxicity were reported in phase I trial studies.[17]

T-CELL CO-STIMULATORY BLOCKERS

Among tolerance inducer methods, affecting signals that lead to T cell activity are of a considerable importance. Co-stimulatory signals are needed to complete T cell response following antigen detection. This is accomplished by T cell surface accessory molecules. Among these, Co-stimulatory, CD28: B7, and CD154: CD40 are of great importance. CTLA-4-Ig is a fusion protein and a CD28 homolog. When it binds to B7 molecule, its interaction with CD28 is blocked.[18] Administering this protein and anit-CD154 in experimental studies proved to be effective in preventing rejection.[19]

Together with this drug, Sirolimus could improve graft tolerance by producing apoptosis signals. These observations are of great clinical importance because they provide selective immunosuppression instead of global immunosuppression.

IMMUNE MODULATION

In these methods, non-specific changes in the immune system facilitate graft acceptance with no impact on effector cells.

1- Donor-specific bone marrow infusion: In this method short-term non-specific immunosuppression leads to long survival of graft with no need to any immunosuppressive. Thus, donor-specific bone marrow cells provide a signal for tolerance.

2- Blood transfusion: This method is of useful impact in increasing survival of transplanted kidney. Microchimerism is one of the mechanisms of bone marrow cell infusion and blood transfusion. The existence of donor cells in recipient blood circulation even in a very low amount is an important factor in tolerance stability.

3- IVIG infusion: It leads to the production of antiidiotyic antibodies and the decrease of anti HLA antibodies if administered prior to transplantation.

4- Photopheresis: It is one of the new treatments in extracorporeal photochemotherapy. It was used in the treatment of T cell cutaneous lymphomas and some autoimmune diseases. In this method, peripheral mononuclear cells were separated by aphresis. These separated cells are exposed to 8-methoxy psoralen and ultraviolet light extracorporeally and again infused to the body. This method had been used in resistant rejections of transplanted heart and kidney and in some types of lung rejection.[20] In one study, four patients with rejected transplanted kidney, which were resistant to conventional treatments, were treated by photopheresis for six months. All rejections were improved and corticosteroid dosages were reduced in three.[12]

In the future, new treatments can considerably increase survival of transplanted organ, and patients will have a hopeful life.

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