Research and Reviews: Journal of Journal of Cholesterol and Heart Disease

Extended Abstract
Vol. 1, Iss.3
2018

Cardiology-2020: Modern immunosuppressive agents after heart transplantation - Maravić-Stojković Vera - School of Medicine Belgrade University Belgrade, Serbia

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Introduction:

Transplantation medicine is a life-saving procedure for patients with end stage organ diseases. Since the first successful kidney transplantation was prepared in the 1950s, and particularly since the introduction of potent and selective immunosuppressive agents in the 1980s, great progress has been made in the graft preservation and patient survival. Heart transplantation (HTx) was at first an excellent experiment on animals, which evolved into a successful therapy for patients with severe heart failure. On a global level, approximately 3,500-4,000 heart transplants are performed annually, half of which in the United States. About 800,000 people have been classified in the NYHA functional Class IV, and most of them are in a waiting list for heart transplant. Over the past twenty years, several studies reported about improved survival rates following the orthotopic HTx: 1-year survival of 88.0 % (males), 86.2% (females), 3- year survival of 79.3% (males), 77.2% (females) and 5-year survival of 73.2% (males), 69.8% (females). The world's longest living heart transplant recipient has been alive and well after 31 years. This increasing success is largely a result of advances in several areas, including (but not limited to):

Tissue typing and donor-recipient matching,

Careful donor evaluation, organ procurement, organ preservation, and recipient preparation;

Perfect surgical technique

Use of antimicrobial prophylaxis or preemptive treatment to prevent infection or its sequels;

Individualized immunosuppression that balances prevention and treatment of graft rejection with minimal risk of toxic side effects;

Replacement of the aggressive immunosuppression with low doses of the synergistic drugs to reduce malignancy.

After HTx, the patient takes immunosuppressive medications throughout the entire lifetime of the graft, i.e. the patient. The main goal is to achieve immunological tolerance, i.e. unresponsiveness of the immune host system to the foreign antigens. Unfortunately, such medicaments are not discovered so far, and the next step is to minimize the risk of organ rejection. To accomplish this task, we use genetic investigations, the procedures which allow us to pick out the analogous tissue antigens between donor and recipient. After appropriate matching and starting the induction immunosuppression, close monitoring and frequent dose adjustment is necessary. In order to detect rejection, the patient is permanently monitored, including regular heart muscle biopsy and some sophisticated blood tests. Usually, biopsy is performed once a week during the first postoperative month (or whenever the rejection is strongly suspected), followed by a more relaxed schedule later on.

The risk of rejection never fully goes away, and the patient needs to receive immunosuppressive agents for the rest of his/her life. This may cause unwanted side effects, such as hyperacute, acute or chronic rejection, as well as posttransplant lymphoproliferative disorders (PTLD), or permanent susceptibility to all kinds of infections. Unfortunately, some recipients developed renal failure or malignant diseases due to the over-aggressive immunosuppressive treatment.

Immunosuppressive Drugs

Immunosuppression has evolved gradually since it was first introduced in the middle of the previous century. Currently available classes: corticosteroids, antimetabolites, poly- and mono-clonal antibodies,

This work is partly presented at 27th International Conference on Clinical & Experimental Cardiology Research September 21-22, 2018 Vancouver, British Columbia, Canada.

calcineurin inhibitors (CNI`s) and proliferation signal inhibitors, have been described

Summary and Conclusions

The ideal immunosuppression should be able to prevent or heal rejection and to lower the risk of infection or cancer to its minimum. There are several ways to achieve this goal: to act specifically by depleting lymphocytes, to act selectively by blocking activation of cells, or to redirect the lymphocyte traffic. The successful solid organ transplantation, particularly in the case of heart and liver, was improved with the introduction of potent IS drugs, particularly CNIs inhibitors.The introduction of cyclosporine in the early 1980s as the backbone of IS regiments, resulted with substantial improvement in the survival of patients with solid organ transplantation. Two decades later other agents were introduced, MMF/MPA with the intention to achieve lowering of the dose of CNIs as maintenance therapy and to prevent early rejection. The biggest movement after 2000 was opportunity to combine several IS drugs as introduction therapy, when alloimune response is most intense. Modern IS agents for induction therapy can be summarized as follows: 1) depleting antibodies (ATG, OKT3, and alentuzumab); or 2) basiliximab or fusion proteins CTLA4-Ig. This can be achieved with or without the use of the induction therapy, which is nowadays used in about one-half of transplant programs. The growing body of evidence rises concerns about the use of OKT3, which is associated with greater risk of lymphoproliferative disorders. The reason for this is the recently acquired evidence of long-term complications linked to certain medications used as induction therapy. This suggests that it is necessary to find the balance between benefit and long-lasting toxicity developed during medical therapy. For this reason, there are suggestions that introducing therapy should be in use selectively only in high sensitized patients.

The most important is maintenance IS therapy with the objective to produce continuous host-graft tolerance with lowering the risk of malignancies and opportunistic infections. All transplant centers have adopted protocols where triple therapy is in use as a maintenance therapy, starting with corticosteroids, one of the CNIs (cyclosporine or tacrolimus) and an antimetabolite, usually MMF. Corticosteroids are generally used early after Tx until the end of first year by slow tapering of the dose. The withdrawal can be eater fast/early or slow/late. In early withdrawal, the prednisone is discontinued within the first month after HTx. Late withdrawal involves the use of prednisolon for at least 6-12 months and has the advantage of more intense immunosuppression in the first six months when rejection rate is at its highest level. Minimal use of steroids and early withdrawal are strongly recommended in pediatric transplantation, as these may impair normal growth.

Modern immunosuppression is directed toward the use two or three drugs with distinct mechanisms of action and different side effects. That way, synergistic potential of the IS drugs is combined to achieve strong antirejection effect but to avoid toxicity. Belatacept and FTY720 are very effective, with no additional toxicities, but capable for synergistic action in combination with other drugs. The final goal is to reduce the number of drugs and to achieve safety in monotherapy. In that regard, it is important to have in mind that each patient is a unique person and that tailoring immunosuppressive agents is a lifelong task after solid organ transplantation.

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