Nephropathy Induced by Calcineurin Blockers in Patients After Heart Transplantation as One of the Important Problems of Modern Transplantation

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Citation

Abstract
This paper addresses the problem of calcineurin blockers nephrotoxicity (cyclosporine, tacrolimus) in patients after heart transplantation. Based on the literature data clinical experience, the authors draw attention to the side effects of the drugs, which in extreme cases can lead to the need for renal replacement therapy. The authors outline the possibility to reduce the risk of this complication mostly by therapy individualization, wider use of induction therapy (anti-inteleukin-2 receptor monoclonal antibodies) and replacement use of mTOR inhibitors. Studies on new drugs are also promising, (e.g. voclosporin), which has low nephrotoxicity and prevents the graft rejection more effectively than CsA.

1. Introduction

Heart transplants are now the treatment of choice in patients with permanent myocardial damage that is resistant to conservative treatment. The most common indications for heart transplantation in adults are advanced cardiomyopathy caused by the progression of coronary artery disease, post-inflammatory cardiomyopathy and terminal stages of severe heart valvular defects. In children, the common causes of entitlement for transplantation include severe congenital heart diseases, various cardiomyopathies (dilated, hypertrophic, restrictive), myocarditis and severe heart failure caused by complex valvular heart diseases. The number of transplants performed is substantial but it is still insufficient due to no sufficient number of donors. Globally, about half of all heart transplants are performed in the U.S. and the remaining part mainly in Europe. Currently in Poland, five transplant centres perform about 100 transplants a year on average (4).

The present results of heart transplantations are good. A one-year survival is over 80%, and a five-year about 70%. Nearly 90% of patients achieve full mental and physical efficiency after transplantation. The vast improvement in efficiency, particularly pointed out in recent years, was possible due to summing of the number of favourable factors such as more experienced transplant teams, an improvement in the transplantation technique and storage of the collected organs, modernization and improved quality of the equipment used for transplants, and finally, what seems most important, the use of more effective suppressive therapy.

The initial, not the best results of transplantation in the 60’s and 70’s of the previous century to a large extent resulted from insufficient immunosuppression which was based
on Imuran and steroid therapy. The use of cyclosporin A was the breakthrough (CsA - the 80’s of the last century). Initially, this drug was combined with steroids; however, even better results were obtained in the treatment using three drugs (CsA + steroids + Imuran). In recent years, more and more centres have been using tacrolimus in place of cyclosporine, which is associated with the reports that such conversion not only improves lipid metabolism in these patients, but also reduces the percentage of acute rejection reactions (1, 8, 11, 13).

Also, at present the vast majority of centres use mycophenolate mofetil in place of Imuran because it was found that its combination with calcineurin inhibitors and steroids results in a statistically significant increase in the percentage of patients who survive the first year after heart transplantation (10, 14). Also, the literature frequently emphasizes the need for an early dose reduction or even discontinuation of steroids, since the benefits of such a decision (normalization of blood pressure, carbohydrate and lipid metabolism, maintenance of bone mass, reduced percentage of infectious complications) generally are greater than the possible risk of the rejection reaction (1, 7).

Also, a number of centres use routinely immediately after heart transplantation an induction with rabbit antimonocyte immunoglobulin (RATG) or interleukin-2 inhibitors (Basiliximab, daclizumab), which is associated with decreased rates of acute rejection episodes, particularly in the first period, and sometimes allows the reduction of the initial dose of steroids or calcineurin blockers (2, 3, 5, 12, 18, 21).

2. Main Body

However, regardless of the therapeutic strategy of individual centres, calcineurin blockers are basic immunosuppressive drugs used in patients after heart transplantation. Their action involves selective inhibition of the immune response. After reaching the cells, the drugs bind to cyclophilin (mainly type A) forming a complex CsaA/tacrolimus + cyclophilin that inhibits calcineurin, the enzyme responsible for the activation of T lymphocytes.

Calcineurin blockers also inhibit the activity of other transcription factors, including cell activation nuclear factor and stimulates the secretion of transforming factor beta (TBF-beta), thereby influencing other immunocompetent cells (macrophages, monocytes, dendritic cells, antigen presenting cells). These drugs also act on the beta lymphocytes, reducing the expression of the ligand molecule CD-40.

However, especially the long-term use of drugs, particularly at high doses, creates the possibility of a number of side effects such as nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia (mainly hypercholesterolemia), hypomagnesaemia, hyperkalaemia, metabolic acidosis and increased cancer predisposition. Gingival hyperplasia and hirsutism are common symptoms in the treatment with cyclosporine, while tacrolimus predisposes to hyperglycaemia, drug-induced diabetes, as well as hair loss and baldness. In some cases, especially after treatment with CsA, hemolytic uraemic syndrome (HUS) may appear, expressed by the presence of blood clots in the vessels of glomeruli and small renal arteries, usually accompanied by haemolytic anaemia, fluid retention and high blood pressure.

Nephrotoxicity is a particularly dangerous consequence of using calcineurin blockers. It may be acute or chronic. Acute nephrotoxicity occurs secondarily as a result of contraction of the intrarenal vessels. The histological examinations reveal isometric vacuolization and the presence of giant mitochondria in the cells of proximal tubules. The process is usually reversible and disappears after reduction or discontinuation of therapy. Chronic nephrotoxicity is a consequence of prolonged, persistent intrarenal vasoconstriction and secondary renal hypoxia of the parenchyma. It is also influenced, among other things, by TGF beta and osteopontin, factors mainly responsible for the fibrosis of renal parenchyma.

Oral cyclosporine doses taken by patients were within a wide range of 0.5-10 mg/kg of body weight per day. Quite often, there is a disproportionate blood concentration of this drug compared with the size of the dose. Therefore, blood levels are monitored, both in the use of CsA and tacrolimus. The so-called C0 is determined - the blood concentration of the drug 12 hours after its oral administration, C1 (2 hours after administration). Sometimes the area under the curve (AUC) is determined, which is the sum of 6 consecutive drug determinations performed within 4 hours after administration (5000 ng/ml on average). It is assumed that the level of C0 for CsA in the initial period after transplantation should be 400 ng/ml, later about 150-250 ng/ml. The recommended blood level of tacrolimus (Co) should initially be in the range of 15-20 ng/ml, later 5-8 ng/ml. Doses of the drug determined depending on the time after heart transplantation and its blood levels usually range from 2 x 0.15 mg/kg of body weight per day to 2 x 0.05 mg/kg.

Treatment with these drugs and according to these rules, in most cases prevents the rejection reaction and minimizes the risk of side effects. Sometimes, however, in no small groups of patients, the prolonged use of these products (mainly CsA) leads to chronic nephropathy with subsequent terminal renal failure.

Over the past several years, we have treated in our centre three patients due to this complication after heart transplantation. One patient underwent successful kidney transplantation; the second one continues dialysis and the third one died after a few years of dialysis due to the worsening circulatory and respiratory failure.

To sum up the presented cases and literature reports we would like to draw attention to the not negligible risk of developing chronic nephropathy after using calcineurin blockers in patients who underwent heart transplantation.
Such a threat is real, despite compliance to the recommended doses of these drugs and not exceeding and monitoring their blood levels.

Paradoxically, when treating these patients in a typical way, in some cases we can violate the basic principle of medicine: firstly, do not harm. Some patients thanks to immunosuppressive therapy are effectively protected against the rejection reaction, and at the same time they are thrown into another clinical disaster, development of chronic nephropathy with the subsequent need for dialysis or kidney transplantation. The importance of this issue is highlighted by a number of authors. Garrido et al. drew attention to the relation between the persistence of high blood CsA levels in patients after heart transplantation and the incidence of chronic renal failure (7). Lindelew et al. evaluated the course of the disease in 200 patients who underwent heart transplants at the Sahigrenska University Hospital in Goteborg, Sweden. During 9 years of observation, the renal function deteriorated in 44% of them. The authors ascribe this mainly to the age of recipients and the suppression used (especially CsA). Interestingly, the use of statins, calcium channel blockers or ACE inhibitors had no statistically significant impact on the renal function (14). Hsu et al. evaluated the renal function in 132 heart transplant recipients who underwent transplantations in the years 1992-2002 in Taiwan. They found a significant increase in the prevalence of chronic renal failure: within 10 years the number of chronic nephropathy increased from the initial 7 to 57% (12). Chronic renal failure is a frequent complication in patients after transplantation, not only after heart transplantation. Ojo et al. evaluated 69321 patients from the US, who underwent non-renal organ transplants in the years 1999-2000. After 5 years, 11426 (16.5%) had signs of chronic renal failure. Depending on the transplanted organ, the percentage of chronic renal failure ranged from 7 (heart and lung transplants) to 21 (intestinal transplantation). The development of renal failure significantly decreased a survival chance in these patients (17).

So, how to solve this complex problem to the benefit of the patient? The answer is not clear. Different authors suggest various types of optimization of the therapy. Multicenter randomized controlled trial conducted in nine transplant centres in the U.S. and Europe in 98 patients after heart transplantation showed a good effect with no nephrotoxicity in the case of using the combined therapy with mycophenolate mofetil and daclizumab (Zenapax) (18).

The literature highlights a particularly beneficial effect of both daclizumab and basiliximab (Simulect) - humanized monoclonal antibodies against interleukiny-2 receptors (anti-IL-2R Ab). These drugs used in the induction treatment delay the administration of the first dose of calcineurin inhibitors in patients after transplantation, reducing the percentage of severe rejection reactions and the risk of cyclosporine-induced nephropathy (2, 7, 13, 18, 21). Many transplant centres more widely use proliferation signal inhibitors (also known as protein mTOR inhibitors) Sirolimus or Everolimus in the immunosuppressive therapy in patients after heart transplantation. They are used alternatively to mycophenolate, primarily for recurrent cellular rejection or intolerance to the drug, especially in patients with a history of cancer or coexisting neoplasm. They are administered to the patients who develop renal failure, interchangeably to calcineurin blockers combined with mycophenolate mofetil or sodium, as they have low nephrotoxicity. Randomized studies conducted in 11 European centres evaluated 83 heart transplant recipients during one year after transplantations. Patients were divided into two groups. Apart from Imuran and steroids, one group received CsA, while the second Sirolimus. During the follow-up period of 8-52 weeks after transplantation, there were statistically significant differences in favour of the group taking Sirolimus (6, 9, 15, 19).

Glucocorticoids are used in heart transplants usually in the perioperative period at high doses (up to 1g of methylprednisolone succinate daily), and then are gradually reduced, usually in terms of the prednisone, from 1 mg/kg/day to less than 2.5 mg/day. It is believed that discontinuation of steroid therapy is possible even at 3 months after heart transplantation, especially when the benefits of this decision (normalization of blood pressure, blood glucose and lipid metabolism, maintenance of bone mass, reduced body weight–steroid-induced Cushing's syndrome, reduced risk of infectious complications) are greater than the risk of acute rejection reactions (1, 7, 10, 11).

To sum up the above data, it seems to us that, as in the treatment of renal transplant patients, also in patients after heart transplantation, the need for individualized immunosuppressive therapy should be in the first place. Therefore, in children and adolescents with immune (post-inflammatory) cause of myocardial damage, with no HLA compatibility between donor and recipient and significantly higher antilymphocyte antibody levels, we should consider from the very beginning, more intensive suppression by ordering the induction (preferably using monoclonal antibodies against IL-2 receptors) with concomitant replacement of CsA with tacrolimus and Imuran with mycophenolate. In order to reduce the risk of development or progress of chronic nephropathy after using calcineurin blockers in patients with primary or secondary impaired renal function, we could propose replacing them with mTOR inhibitors or the administration of high (under blood level control) mycophenolate doses, with a minimized dose of CsA or even better tacrolimus (preferable Co level of CsA would fluctuate between 100 ng/ml, tacrolimus 3-4 ng/ml). Possible rejection reactions could be suppressed by the administration of methylprednisolone infusions, polyclonal (ATG, Thymoglobulin) or monoclonal (OKT-3) antibodies. It also seems that in the future, IL-2 receptor blockers will play a greater role in the induction. There is still a striving to gain more and more effective immunosuppressive drugs, which at the same time would minimize side effects, especially nephrotoxicity. Currently, Phase II and III clinical trials are being conducted which study drugs in the form of small particles such as voclosporin, JAK-3 inhibitor (CP-690 550), protein kinase inhibitor AEB-071 and Bortezomib—a
humoral response inhibiting agent. Also, biological agents are being tested: co-stimulation blocker-Belatacept and a monoclonal antibody against adhesive molecules (Efacizumab). It seems that voclosporin (ISA-247) is the most promising future-oriented medicine, a semi-synthetic analogue of cyclosporine, but having a stronger inhibitory effect on calcineurin and lower nephrotoxicity (3, 16, 20). In conclusion, we would like to emphasize that optimization of the immunosuppressive therapy in patients after heart transplantation is still a difficult and unsolved problem.

It requires a lot of clinical experience and a thorough diagnosis (including, among other things, monitoring blood levels of immunosuppressive drugs, intravascular Doppler assessment of the coronary arteries, control coronary testing, rapid and reliable assessment of the puncture material from the myocardium, etc.).

The above reports are our voice in the discussion, since this issue surely requires further clinical studies and multicenter comparisons.

3. Conclusion

This approach to the treatment of patients after heart transplantation is based on individualized therapy and the possibility to choose from a wide range of drugs and immunosuppressive regimens those the most beneficial for an individual patient together with determining an optimal dose. We hope that this practice may minimize the risk of adverse effects of these drugs, including nephrotoxicity and protect, at least some patients, against development of chronic renal failure.

References


