REVIEW ARTICLE

Calcineurin inhibitor sparing immunosuppressive regimens in kidney allograft recipients

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KEY WORDS

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ABSTRACT

Calcineurin inhibitors (CNI), cyclosporine and tacrolimus, have had a potent impact on the success of organ transplantation. However, the nephrotoxicity associated with CNI can cause renal dysfunction, which is an independent risk factor for graft loss and mortality after kidney transplantation (KTx). Thus, the search for an optimal immunosuppressive therapy continues to be crucial in KTx. Strategies to limit CNI exposure include CNI minimization, avoidance, and withdrawal. We conducted a literature review (PubMed, Medline) on this issue. Maximum reduction in CNI is associated with a modest improvement in renal function; however, the kidney damage is observed as long as CNIs are maintained. Avoidance of CNI is associated with high acute rejection rates. CNI withdrawal may be the optimal strategy because it reduces early immunologic graft injury after KTx, particularly when CNI withdrawal is initiated before irreversible renal damage. These strategies seem feasible with mycophenolate acid, sirolimus and induction therapy with interleukin-2 receptor antibodies as concurrent immunosuppressants.

INTRODUCTION Improved outcomes of organ transplants observed over recent years have been possible due to advances in clinical immunology, new surgical techniques in organ harvesting, preservation and transplantation, new immunosuppressive drugs and the modification of immunosuppressive protocol.[1]

Since cyclosporine A (CsA) was introduced into clinical practice in the early 1980s, risk of acute rejection episodes has dramatically decreased. Despite reduced acute rejection rate and improved 1-year survival for kidney transplant, long-term results have not changed. Transplanted organ survival rate has remained unchanged for years and 10-year graft survival curves following kidney transplantation (KTx) are identical to those from pre-cyclosporine era when annual kidney graft loss rate was 3–5%.[2]

An increase in the number of transplanted organs in high-risk patients[3] or organs from extended criteria donors[4] may be responsible for the lack of improvement. It cannot be excluded, however, that an aggressive immunosuppression protocol, while reducing the rate of acute rejection episodes, increases the risk of opportunistic infections or malignancies. This may cause kidney graft loss in the late posttransplant period. Polyoma BK virus nephropathy observed over recent years could serve as an example.[5] Side effects induced by specific immunosuppressive drugs and particularly nephrotoxicity of calcineurin inhibitors (CNI), including cyclosporine and tacrolimus, account for lack of improvement in long-term graft survival. Sings of CNI nephrotoxicity are observed in almost all patients after 10 years of treatment.

Nankivell et al. reported nephrotoxicity during CsA treatment in 12.6% of protocol biopsies performed in the early post-KTx period; such abnormalities were observed in 53% of protocol biopsies after first posttransplant year, and in 67.3% after 5 years. 10 years after KTx, late CsA nephrotoxicity was observed in all protocol biopsies.[6]

One of the currently applied strategies to improve long-term outcomes in patients after KTx

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is optimization of immunosuppression, which responds to the needs of individual patients in terms of the number, dosage and type of immunosuppressive drugs used in the treatment.[7]

Calcineurin inhibitor nephrotoxicity CNI, which selectively inhibit interleukin-2 (IL-2) dependent lymphocyte T activation and proliferation, are the main non-immunological cause of chronic allograft dysfunction. This complication accounts for about 50% of kidney graft loss in the late post-KTx period.[8]

Nephrotoxicity is observed not only in transplanted kidneys but also in native kidneys in patients who receive CNI treatment after other organ transplant or in patients suffering from autoimmune diseases. Renal failure in these groups ranges from 7 to 21%, depending on the transplanted organ.[9]

Acute, reversible nephrotoxicity accompanying CNI therapy results from the imbalance in vasoactive substance release. The administration of CNI causes vasoconstriction of both the afferent and, to a greater degree, the efferent arterioles, which leads to a decrease in renal blood flow and glomerular filtration rate (GFR), and an increase in renal vascular resistance. Kidney biopsy histopathology shows characteristic isometric vacuoles in proximal and distal tubular cells. CNI cause glomerular capillary and arteriolar damage, and disseminated thrombosis in microvessels.

Chronic CNI nephrotoxicity is caused by immunological and non-immunological damage. Histopathological examination shows renal tubular atrophy with typical microcalcification, patchy fibrosis and nodular arteriolar hyalinosis. According to Mihatsch, arteriolopathy, the main symptom of CNI nephrotoxicity, is a variant of thrombotic microangiopathy with slow, subclinical course. Differentiation between arteriolar hyalinosis associated with CNI administration and arteriolar sclerosis in hypertension, diabetes, or the elderly poses a challenge. A typical feature of CNI toxicity is substitution of smooth muscle cells by hyaline deposits in the external media layer; while in arteriolar hyalinosis in other clinical situations the smooth muscle cells are intact and hyaline deposits accumulate beneath the endothelium.[10] There is no precise classification to assess CNI nephrotoxicity; that is why new scales and classifications are developed in order to enhance the precision of diagnosing CNI nephrotoxicity. The new scales to evaluate CNI nephrotoxicity, like the older ones, show arteriolar hyalinosis as the most typical abnormality.[11]

Chronic lesions and acute nephrotoxicity in CNI treatment are caused by various mediators, including renin–angiotensin–aldosterone (RAA) system, which by activating angiotensin type 1 receptor is not only a contributory factor in renal vascular bed constriction, but also influences kidney fibrosis and aldosterone release. Activation of RAA system through CNI may cause harmful hemodynamic (vasoconstriction) and nonhemodynamic changes (via enhanced synthesis of transforming growth factor-β, vascular endothelial growth factor and enhanced renal cell apoptosis).[12] The CNI-induced TGF-β formation produces tubulointerstitial fibrosis by increased synthesis and decreased extracellular matrix degradation.[13] Administration of losartan, AT1 blocker, in kidney transplant patients leads to a significant decrease in TGF-β serum levels and increased GFR.[14]

Recent trials have shown that aldosterone, the final product in the RAA system, may play an important role in CNI nephrotoxicity; therefore, spironolactone administration may be an effective strategy in the prevention of CNI nephrotoxicity.[15]

During CNI treatment, disturbances in nitric oxide (NO) release and NO synthase activity may generate reactive oxygen species; all of them might be involved in tubular epithelial to mesenchymal transition.[16,17]

Protein kinase C (PKC-β) contributes to CNI dependent fibrosis. It has been proved that CsA administration enhanced PKC-β mRNA and protein expression; adding hispidine, a PKC-β inhibitor, inhibited TGF-β1 synthesis in proximal tubule cells.[18]

Cyclosporine increased expression of transcription factors participating in malignant transformation, including mRNA for transcriptive factor EA2, and the transcription factor Pax8. Many other genes, involved in cancer development showed enhanced expression under CsA treatment.[19] Cyclosporine may induce phenotype alterations of malignant cells, thus making them more invasive. It has been shown that adenocarcinoma cells in CsA treated patients have morphological features such as cell membrane invaginations and projections, which increase cell mobility and capability of anchoring and growth. These alterations were inhibited by anti-TGF-β treatment.[20]

According to the theory proposed by Meneghin and Hogaboam, the development of fibrosis in a transplanted organ may also be caused by chronic infection, which drives the immune system for a long time. The authors suggest that persistent fibroblast exposure to pathogen-associated molecular patterns (PAMP) maintains these cells in a constant, unrestrained activation. PAMPs are pathogenic byproducts such as lipoproteins, bacterial DNA and double-stranded RNA, which are recognized by their receptors (pattern recognition receptors – PRR) and are expressed on a number of cells including fibroblasts. These receptors also include Toll-like receptors (TLRs). Interaction between PAMP and PRR serves as the first line of defence during infection and activates many inflammatory cytokines and chemokines. Chronic infection leads to persistent PAMP synthesis and immune system activation. Meneghin and Hogaboam postulated that PAMPs – TLR ligands – which directly stimulate TLR presented on fibroblasts, leading to excessive profibrotic cytokine excretion. The authors

suggested that inhibition of pathogen related fibroblast activation might effectively prevent or diminish fibrosis in the kidney allograft.[21]

CNI may exert adverse cardiovascular effects because of their influence on arterial hypertension and lipid disorders. The drugs have diabetogenic properties which are enhanced in combination with glucocorticosteroids (GS).[22] Other metabolic complications during CNI treatment include high bone turnover and osteoporosis.[23] Neurotoxicity of CNI commonly manifests itself in the form of headache, insomnia, limb tremor, but may also cause life-threatening neurologic complications.[24] Therefore, we stress the need to develop strategies reducing CNI toxicity or to use CNI-sparing immunosuppressive regimens.

Calcineurin inhibitor treatment optimization Dose optimization to reduce side effects of CNI has been studied for many years. Various strategies have been used, including complete CNI avoidance, dose reduction in *de novo* transplant patients, late CNI introduction and dose reduction or withdrawal in the long-term posttransplant period. In the latter case, drugs were withdrawn/dose reduced as prevention of advanced allograft nephropathy, or when patients had indications for CNI minimization. The drug was withdrawn abruptly or gradually. Below is a literature review of relevant clinical trials we selected.

Calcineurin inhibitor treatment optimization in azathioprine treated patients Early cyclosporine A withdrawal In metaanalysis of 10 randomized and 7 non-randomized trials, early withdrawal of CsA in azathioprine (Aza) and prednisone (P)-treated patients showed that CsA withdrawal had no impact on the 1-year patient and graft survival, although acute graft rejection rate increased significantly by 11% ($p < 0.001$).[25]

The results of a 15-year-long study with CsA withdrawal after 3 months post-KTx were demonstrated by Australian authors. In the years 1983–1986, they randomized KTx patients to one of 3 groups: a group on Aza/P treatment (n = 158), a group on CsA/P (n = 166) and a group with CsA/P administered for a short period with subsequent conversion to Aza (n = 165). They did not observe any significant differences in 15-year patient survival in the above groups (48% vs. 56% vs. 51% $p = 0.14$) and 15-year death-censored graft survival rates were 47% vs. 44% vs. 59%, respectively; $p = 0.06$. In the group which had CsA withdrawn 3 months after transplantation, significantly lower creatinine level (143 vs. 169 vs. 131 μmol/l $p = 0.04$) was observed. In the CsA group kidney graft loss was higher (58/166) than in the group without CsA (33/165). Similarly, the risk of developing cyclosporine-induced chronic nephrotoxicity was higher in the CsA group (62% vs. 28%).[26]

Late cyclosporine A withdrawal Early CsA withdrawal in Aza treated patients was associated with higher acute rejection rate. Thus, attempts were made to discontinue CsA in the late post-KTx period in stable patients without previous acute rejection episodes. Heim-Duthoy et al. tried to withdraw CsA in 192 long-term posttransplant patients. The CsA dose was gradually reduced, and previous doses of GS and Aza were increased. Frequency of acute rejection in patients after CsA withdrawal was 9.1%; 5-year graft survival in the CsA and non-CsA groups did not differ significantly and was 81.7% in the group which continued CsA treatment and 81.5% in the group which had CsA gradually withdrawn over the period of 12 weeks.[27]

Scottish authors have recently presented 15-year results of CsA discontinuation and conversion to Aza after 1 year post-KTx. They randomized 216 patients with creatinine level <300 μmol/l and no acute rejection during 6 months prior to randomization to one of 2 groups: group 1 with continued CsA treatment (n = 114) and group 2 with Aza introduction after CsA discontinuation (n = 102). They did not observe any differences in patient survival after 15 years (62.4% in the CsA group vs. 64.4% in the Aza group, not significant [NS]). Graft survival after 15 years was 41.9% in the CsA group and 48.8% in the Aza group (NS). Ten-year posttransplant patients in the CsA group demonstrated worse renal graft function and developed arterial hypertension more often.[28]

Calcineurin inhibitor treatment optimization in mycophenolate mofetil-treated patients Calcineurin inhibitor avoidance Among the first authors who avoided CNI in immunosuppressive regimen with mycophenolate mofetil (MMF) were Vincenti et al. They used 5 doses of daclizumab combined with MMF (3.0 g for at least 6 months) and a standard dose of GS in 98 low-immunological risk patients. Acute rejection rate was 48% after 6 months and 53% after 12 months.[29]

A similar, prospective, non-randomized trial with the use of daclizumab/MMF 3.0 g/day/GS in 45 low-immunological risk patients was conducted by Tran et al. In the case of acute rejection or MMF intolerance (51% of the studied patients) CsA was introduced. Patients who did not require CNI administration had lower creatinine levels 6 months after transplantation and took lower doses of antihypertensive drugs. Biopsy-proven, acute rejection episodes were diagnosed in 31% of patients. One-year graft and patient survival was 95 and 100%, respectively.[30]

In conclusion, in studies on CNI avoidance, in patients receiving MMF even in combination with IL-2-receptor blockers or polyclonal anti-T antibodies, acute rejection rate was too high to accept this strategy of CNI-sparing.

Calcineurin inhibitors withdrawal **Early calcineurin inhibitor withdrawal** Hazzan et al. randomized 108 patients to one of 2 groups 3 months after KTx: group 1 had CsA withdrawn (the MMF group, n = 54), group 2 had MMF discontinued

(CsA group, n = 54). In both groups drug withdrawal was quick, 25% of the full drug dose was reduced per week. After 2 years, the authors observed that although acute rejection episodes occurred more often in the group without CsA (18.5% and 5.6% in the MMF group and the CsA group, respectively; p = 0.045), transplanted kidney function was better and 2-year graft survival was comparable to the CsA group (98% in the CsA group vs. 93% in the MMF group [NS]). Risk factors for acute rejection included borderline changes in protocol biopsies performed before randomization and a low area under the concentration-time curve (AUC) for mycophenolic acid (MPA). Differences in the frequency of chronic allograft nephropathy (CAN) between the two groups were not observed. In the group without CsA, C4d deposits were observed more often and this was not associated with the previous occurrence of acute rejection.[31]

In a multicenter trial Abramowicz et al. replaced Aza with MMF or *de novo* introduced MMF in 170 patients who initially received GS/CsA with or without Aza. After 3 months from conversion to MMF, they randomized patients to either GS/MMF or GS/MMF/CsA scheme. After 5-year follow-up, acute rejection rate in the GS/MMF group was still significantly higher than in the GS/MMF/CsA group (p = 0.028). After 5 years patient and graft survival were comparable in both groups, but the trend was more beneficial in the group which continued the CsA therapy. In the group on GS/MMF a better renal graft function was mainted (p = 0.05).[32]

The analysis of the above studies shows that early CNI discontinuation in patients receiving MMF in maintenance therapy, but without monoclonal or polyclonal antibody induction, is not a strategy worth recommendation because of a higher acute rejection rate compared to the group which continued CNI therapy. Antibody induction therapy preceding early CNI discontinuation or CNI withdrawal in the later post-KTx period could possibly be safer.

Late calcineurin inhibitor withdrawal Smak Gregoor et al. discontinued CsA and randomized patients with stable kidney graft function, receiving P/CsA after at least 12 months post-transplantation to one of 2 groups: group 1 receiving P/MMF (n = 34) and group 2 receiving P/Aza (n = 30). After CsA withdrawal, acute rejection was observed in both groups, although more commonly in the group converted to Aza (36.7%) in comparison to the group converted to MMF (11.8%); p = 0.04. A significant improvement in kidney graft function was observed in both groups. The frequency of chronic allograft nephropathy was similar in both groups.[33]

One of the first studies with CNI withdrawal (CsA/tacrolimus) and MMF administration was the Suwelack et al. survey[34], in which patients had clinical and biopsy-proven progression of CAN. In this trial, 7 years on average after KTx, 39 patients with CAN, receiving GS/CNI as maintenance therapy were prospectively randomized to one of 2 groups. Group 1 had MMF included in the therapy (n = 20); in group 2 MMF was also administered and CNI was gradually discontinued over 32 weeks following randomization (n = 19). In patients who received MMF/GS therapy without CNI, kidney graft function improved compared to the group which continued CNI therapy (p = 0.002).[34]

Calcineurin inhibitor dose reduction **Early calcineurin inhibitor reduction** In the CAESAR study, 3 immunosuppressive regimens were compared:

1 daclizumab/MMF/GS + reduced CsA dose in the early period, and subsequent CsA withdrawal;

2 daclizumab/MMF/GS + reduced CsA dose maintained through the entire follow-up;

3 MMF/GS + standard CsA dose, without daclizumab.

There were no differences in GFR, 12 months post-KTx in the examined groups, but the percentage of patients with acute rejection was highest in the group with CsA withdrawn. The analysis of the group which had CsA withdrawn revealed that these patients had a high risk of acute rejection when AUC for MPA was <30–40 μg/h × ml. In the case of AUC for MPA >60 μg/h × ml, the percentage of patients with acute rejection was similar to the group continuing CsA treatment.[35]

Equally positive results were observed in the "Reference Study", in which CsA was decreased by ½ and maintenance therapy was continued with MMF and GS. Following CsA dose reduction, creatinine clearance improved by 11% at 2-year follow-up. There was no acute rejection after CsA dose reduction.[36]

Late calcineurin inhibitor reduction Pascual et al. randomized 64 patients with stable graft function to one of 2 groups, 12 months post-KTx: group 1 with the CsA dose reduced by ½ (n = 32) and a full CsA dose continuation (n = 32). Both groups underwent maintenance therapy with GS/MMF. The study results were promising, namely, in the group with the CsA dose reduced by ½ significant improvement in creatinine clearance 6 months after intervention was observed (clearance increased by 6.9 ml/min). There were no acute rejection episodes during follow-up in the studied groups. Only in the group with a reduced CsA dose, arterial blood pressure control, lipid profile and uric acid level improved.[37]

In Garcia et al. the group of 169 patients (153 on CsA and 14 on tacrolimus) with CAN (57% cases were biopsy-proven) were converted from Aza to MMF with simultaneous CNI withdrawal (n = 66) or CNI dose reduction (n = 103). In both groups improvement in kidney graft function was observed. There was greater improvement in the group with CNI withdrawn than in the group with the CNI dose reduced.[38]

Calcineurin inhibitor therapy optimization in patients treated with sirolimus The use of immunosuppressive regimens with sirolimus and a full CNI dose may impair transplanted kidney function and renal graft survival. It is associated with an increase in CNI nephrotoxicity induced by sirolimus.[39,40] An immunosuppressive regimen with CNI discontinuation in sirolimus treated patients may be beneficial.

In a prospective RMR trial (Rapamune Maintenance Regimen), 430 patients on sirolimus/CsA/GS were randomized to one of 2 groups 3 months post-KTx; in group 1 CsA was discontinued and sirolimus/GS were continued (sirolimus level: 20–30 ng/ml), in group 2 initial immunosuppressive regimen was maintained. After 2 years, there were no significant differences in acute rejection rate between the groups (there were no late acute rejection episodes), patient and graft survival were similar. In the group with CsA withdrawn, improved kidney graft function and blood pressure control were observed. After 48 months, the results were better in the group receiving sirolimus/P compared to the group receiving sirolimus/CsA/P (graft survival was 91.5% and 84.2%, respectively; $p = 0.024$). GFR was also significantly higher in sirolimus/P vs. sirolimus/CsA/P (58.3 ml/min vs. 43.8 ml/min, $p < 0.001$). Acute rejection rate was comparable in both groups. Mean arterial blood pressure was lower in the group without CsA ($p = 0.047$). The analysis of protocol biopsies performed after 36 months of study showed lower chronicity score in the group receiving sirolimus/P compared to the group on sirolimus/CsA/P. In the sirolimus group, lower overall malignancy rate (particularly involving the skin and other organs) was observed; cancer occurred later than in the CsA group. It should be underlined that non-adherence with the study protocol was higher in the sirolimus group, after 2 years (48 vs. 38%) and also after 4 years of follow-up (60.9 vs. 44.2%).[41]

In another multicenter study, 197 patients were randomized to one of 2 groups: group 1 with a full CsA dose and a fixed, 2 mg sirolimus dose ($n = 97$) and group 2 with a reduced CsA dose and a sirolimus dose adjusted to the target level of 10–20 ng/ml ($n = 100$). At the end of the 2nd month of the study, CsA was completely withdrawn in group 2 (in the case of no acute rejection episode). After 12 months of observation patient and graft survival were similar in both groups; but in group 2, better kidney graft function was observed. Acute rejection rate in groups 1 and 2 was 18.6 and 22%, respectively; $p = 0.58$.[42]

Sampaio et al. presented similar results in patient and kidney graft survival, and a comparable percentage of acute rejection in tacrolimus group with either MMF ($n = 50$) or sirolimus added ($n = 50$). Compared to the MMF group, the authors observed significantly higher creatinine ($p = 0.007$) and cholesterol ($p = 0.03$) levels in the sirolimus group. There was also a higher percentage of patients with proteinuria ($p = 0.041$), and this abnormality was also more pronounced ($p = 0.001$).[43]

When conversion from CNI to sirolimus is indicated because of CAN, it should be performed early enough and is recommended when the creatinine level does not exceed 2.5 mg/dl. Conversion should be performed primarily in patients at low immunological and high cancer risk and avoided in high metabolic risk patients with proteinuria >0.8 g/d. CNI should be reduced gradually over 3–6 months, withdrawal should be slow, protocol biopsy control is indicated.[44]

Calcineurin inhibitor treatment optimization in patients treated with mixed immunosuppressive protocols In the study on 44 kidney allograft recipients assessing the efficacy of immunosuppressive protocol without GS, with alemtuzumab as an induction therapy and a reduced tacrolimus dose (tacrolimus level: 5–7 ng/ml) and MMF (2×500 mg) as a maintenance therapy, creatinine clearance after 12 months was good and was about 75 ml/min. Patient and graft survival was 100%.[45]

Immunosuppressive MMF/sirolimus protocol was assessed in the group of 254 patients with stable graft function, in whom CNI (cyclosporine or tacrolimus) were discontinued between 30 to 180 days after KTx. In this study (Spare the Nephron), Person et al. observed a 20% increase in GFR in the group receiving MMF/sirolimus/P, and only a 4.4% increase in GFR in the CNI group after 12 months.[46]

In the CONCEPT trial which was conducted in France and involved CNI withdrawal in stable patients 3 months after KTx and their replacement with sirolimus, GFR improvement after CNI discontinuation was observed ($p = 0.01$).[47]

Flechner et al. showed long-term outcomes of a prospective, randomized study assessing the efficacy of immunosuppressive regimen with sirolimus/MMF/GS together with basiliximab induction. They observed similar 5-year patient and graft survival, comparable acute rejection frequency in the group with sirolimus/MMF and the group receiving CNI. After 5 years of observation, GFR was significantly higher in the sirolimus group vs. the CNI group (66.7 ml/min vs. 50.7 ml/min, $p = 0.0075$). After 5 years, 6 *de novo* malignancies were observed in the CNI group (3 solid organ cancers, 3 skin cancers) vs. 2 *de novo* malignancies in the sirolimus group (1 skin cancer, 1 leukemia).[48]

The use of everolimus in immunosuppressive regimens with a reduced CNI dose resulted in improved kidney graft function and increased transplant and patient survival.[49]

In the analysis performed by Srinivas et al., acute rejection episodes and delayed graft function occurred significantly more often, and graft survival rate was lower in 2040 patients receiving sirolimus/MMF compared to other immunosuppressive protocols.[50]

An alternative for mTOR (Target of Rapamycine) inhibitor as a substitute for CNI could be belatacept, a costimulatory signal blocker. Combined with MMF/GS and basiliximab, the drug was compared to standard immunosuppression with GS/MMF/CsA; initial results were encouraging – no higher acute rejection rate was observed in the belatacept group. Compared to the CsA group, higher GFR values and a lower percentage of patients with CAN were observed.[51] Currently, we are waiting for the results of the BENEFIT (Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression) and BENEFIT-EXT (Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression-Extension) studies on the role of belatacept in the prevention of CAN.

In the ELITE-Symphony Study (Efficacy Limiting Toxicity Elimination), 1645 patients after KTx *de novo* were randomized to one of 4 groups: group 1 receiving a standard dose of CsA/MMF/GS; group 2 receiving daclizumab induction, a low dose of CsA/MMF/GS; group 3 also receiving daclizumab induction, GS/MMF/reduced tacrolimus dose; and group 4, which instead of CNI received a low dose of sirolimus. Twelve months posttransplantation, GFR was highest in patients receiving a low tacrolimus dose (65.4 ml/min) compared to other groups (56.6–59.4 ml/min). Biopsy-proven, acute rejection rate was lowest in the group receiving tacrolimus (12.3%) in comparison to groups receiving a standard CsA dose (25.8%), low CsA dose (24%), and low sirolimus dose (37.2%). One-year kidney graft survival differed significantly between the groups ($p = 0.02$) and was highest in the group receiving a low tacrolimus dose (group 3 – 94.2%). In the remaining groups the results were as follows: group 1 – 89.3%, group 2 – 93.1%; and group 4 – 89.3%. Important side effects occurred significantly more often in patients receiving a low sirolimus dose (53.2%) vs. other examined groups.[52]

SUMMARY The analysis of papers on CNI dose optimization has shown that trials of CNI withdrawal/reduction are associated with an increased risk of acute rejection episode (11–40% on average). At the same time, the study results indicate improvement or at least stabilization of kidney graft function measured by creatinine clearance, or by the calculated GFR, and improvement or stabilization of histopathologic pattern. The rate of acute rejection episodes was higher in patients who received Aza (36%) vs. MMF (12%). Graft and patient survival were often similar between the groups which had CNI withdrawn compared to patients who continued the CNI treatment. This provides a valid reason for the continuation of studies on CNI minimization. CNI withdrawal in a later post-KTx period (at least after 3 months) seems to be safer than complete CNI avoidance and carries a lower risk of acute rejection. Late CNI withdrawal did not always result in graft function improvement, most likely because they were withdrawn when kidney tissue had already been severely damaged. Administration of a reduced CNI dose in the early post-KTx period, precisely monitored using both traditional measurement and protocol biopsy, might possibly produce positive results. If no acute rejection in protocol biopsies is observed after CNI dose reduction, complete withdrawal can be considered. CNI discontinuation should be gradual to minimize the risk of late acute rejection. CNI withdrawal trials should be undertaken in low-immunological risk patients, who received monoclonal or polyclonal antibodies as induction therapy. In maintenance therapy a combined immunosuppressive protocol should be applied: MMF/GS or sirolimus/GS.

Two-year results assessing the efficacy of MMF/sirolimus combination are promising. However, reports on the greater frequency of delayed graft function, impaired wound healing, spermatogenesis disturbances, or an increased rate of proteinuria during sirolimus treatment suggest that one should be cautious about applying this protocol in *de novo* patients after KTx and wait for the long-term results concerning the application of this protocol.[53]

In each type of immunosuppression, if an attempt to discontinue CNI is made, the doses of the remaining immunosuppressive drugs in the maintenance therapy should be at a sufficient level with blood monitoring therof.[54]

It should be underlined once more that CNI withdrawal applies to selected groups of low-immunological risk patients; it would be reasonable to plan this intervention in a prospective manner. In the remaining patients, CNI should be considered as strategic drugs in immunosuppressive protocols.[55]

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Protokoły leczenia immunosupresyjnego ograniczające stosowanie inhibitorów kalcyneuryny u chorych po przeszczepieniu nerki

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immunosupresja, inhibitory kalcyneuryny, leczenie „oszczędzające" stosowanie CNI, nefrotoksyczność, przeszczepienie nerki

STRESZCZENIE

Inhibitory kalcyneuryny (*calcineurin inhibitors* – CNI), cyklosporyna oraz takrolimus, istotnie przyczyniły się do poprawy wyników przeszczepianych narządów. Nefrotoksyczność związana ze stosowaniem CNI może jednak doprowadzać do rozwoju przewlekłej dysfunkcji przeszczepionej nerki, która jest niezależnym czynnikiem ryzyka utraty przeszczepu oraz śmiertelności chorych. W dalszym ciągu poszukuje się optymalnego schematu immunosupresyjnego u chorych po transplantacji nerki (*kidney transplantation* – KTx). Strategie pozwalające na ograniczenie ekspozycji na CNI polegają na: stosowaniu zredukowanych dawek CNI, unikaniu stosowania CNI, oraz na stosowaniu CNI we wczesnym okresie po KTx, a następnie odstawianiu ich w późniejszym okresie po przeszczepieniu. W prezentowanym artykule przedstawiono przegląd piśmiennictwa (PubMed, Medline) dotyczący tego zagadnienia. Stosowanie zredukowanych dawek CNI związane jest z poprawą czynności nerki przeszczepionej, jednak ich kontynuowanie może doprowadzać do dalszego uszkodzenie przeszczepionego narządu. Unikanie stosowania CNI związane jest z istotnym wzrostem częstości występowania ostrego odrzucania. Najlepszą strategią wydaje się odstawienie CNI. Obserwuje się wówczas redukcję częstości występowania procesu ostrego odrzucania we wczesnym okresie po KTx, szczególnie gdy odstawianie ma miejsce w okresie, kiedy nie doszło do nieodwracalnego uszkodzenia przeszczepionej nerki. Strategie te mogą z powodzeniem być zastosowane u chorych leczonych pochodnymi kwasu mykofenolowego, sirolimusem, z indukcją za pomocą przeciwciał przeciwko receptorowi dla interleukiny-2, jako równoczesnym leczeniem immunosupresyjnym.

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