FORTY YEARS OF CYCLOSPORINE IN CLINICAL PRACTICE

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Abstract

Cyclosporine (CsA) was discovered in the lab of Sandoz in Switzerland in 1972. while searching for an antifungal drug. However, it quickly became an irreplaceable immunosuppressive drug for renal and other solid organ transplantation. It has been found, in the initial experiments, that CsA inhibits both in vitro cell-mediated lysis and lymphocyte sensitization by allogeneic target cells. Clinical trials have demonstrated better one-year graft survival after cadaveric renal transplants when receiving CsA instead of azathioprine. Although improvement has been observed in the rates of one-year renal graft survival and acute rejection, but long-term graft survival rate did not improve. This can be attributed to the nephrotoxic effects of the CsA. This issue is a consequence of hemodynamic effects on renal blood flow and glomerular filtration, effect on renal tubular function and blood vessels. Along with nephrotoxicity, CsA also causes other adverse effects such as hypertension, gingival hyperplasia, hyperkalemia, hypomagnesemia, hyperlipidemia, neurotoxicity, and in some cases thrombotic microangiopathies. However, in recent years CsA nephrotoxicity has been looked at from a different angle, where it has been linked to high CsA doses that used to be administered. Following its use in solid organ transplantation, CsA has been found to have an important role in treating systemic connective tissue diseases, as well as its consequences, primary glomerulonephritis, inflammatory bowel disease, and psoriasis. CsA effectiveness in treating above mentioned diseases is still greater than its side effects, which makes it a basis of treatment options for numerous diseases.

Keywords: cyclosporine, transplantation, nephrotoxicity, glomerulonephritis, psoriasis, inflammatory bowel disease

Introduction

Cyclosporin (CsA) was discovered in 1972 and quickly became a revolutionary advancement in the field of transplantation medicine. It led to a significant reduction in the frequency of acute rejections and improved the survival of transplanted organs[1]. Initially investigated as an antifungal agent, it was later found to possess potent immunosuppressive properties effective in solid organ transplantation. Recognizing the crucial role of cellular immunity in autoimmune diseases and chronic inflammation, Borel conducted a series of experiments with immunosuppressive, anti-inflammatory drugs, and antimetabolites to examine their effects on lymphocyte-mediated immune events. These experiments demonstrated that CsA strongly inhibits both in vitro cell-mediated lysis and the activation of lymphocytes by allogeneic cells. Simultaneously, it exhibited a significantly improved safety profile compared to immunosuppressants of that time[2]. Following that, a European multicenter study compared the effectiveness of CsA and azathioprine, demonstrating significantly better the one-year survival of transplanted kidneys from brain-dead donors when patients received CsA (72% *vs.* 52%). This contributed to obtaining approval for its use in the clinical practice of solid organ transplantation[3]. Due to these findings and the fact that CsA substantially reduces the frequency of acute rejections, this medication became a cornerstone in immunosuppressive protocols after solid organ transplantation. Thanks to the use of CsA, one-year survival of transplanted kidneys from living donors exceeds 95%. Unfortunately, the long-term survival of the allograft has not significantly improved, and one of the reasons is believed to be the nephrotoxicity of cyclosporine. This complex issue can be divided into six categories: 1) Hemodynamic Effects on Renal Blood Flow (RBF) and Glomerular Filtration Rate (GFR); 2) Effects on Renal Tubules; 3) Effects on Blood Vessels; 4) Hypertension; 5) Long-Term Toxicity on Renal Interstitium; 6) Association of Nephrotoxicity with CsA Dosage and the dosage of CsA[4].

Effect of cyclosporine on renal flow blood and glomerular filtration rate

Experimental studies have demonstrated that the infusion of CsA immediately after administration leads to a reduction in Renal Blood Flow (RBF) and Glomerular Filtration

Rate (GFR). Similar decreases in RBF and GFR occur after prolonged administration of CsA[5]. Patients undergoing kidney transplantation who receive CsA experience a reduction in RBF and, to a lesser extent, GFR. These changes tend to disappear after discontinuation of CsA administration. Switching from cyclosporine to other immunosuppressive drugs results in a decrease in serum creatinine concentration in kidney transplant patients, and similar results have been observed in autoimmune diseases treated with CsA[6]. These adverse effects of CsA are believed to be mediated by prostaglandins produced in the kidneys and the renin-angiotensin-aldosterone system.

The effect of cyclosporine on tubule function

By increasing the fractional excretion of magnesium, CsA leads to hypomagnesemia. Simultaneously, it causes a reduction in potassium excretion, resulting in mostly mild hyperkalemia without clinical consequences[5]. During CsA administration, there is a decreased excretion of hydrogen ions, which can lead to clinically significant acidosis, especially in patients with kidney insufficiency[7]. Due to reduced uric acid excretion, its concentration increases in the serum, serving as a potential marker for CsA nephrotoxicity. In addition to functional disturbances, CsA induces morphological changes such as vacuolization and atrophy of tubules, as well as striped fibrosis of the interstitium[4].

Cyclosporine effects on blood vessels

Experimental studies on spontaneously hypertensive rats have shown that CsA can cause proliferative and exudative changes in the walls of blood vessels[8, 9]. In a small number of patients, similar changes have been observed in blood vessels, resembling those described in hemolytic-uremic syndrome with thromboses in small blood vessels and glomeruli of the kidneys[10]. Obliterative vasculopathy with intimal thickening may result from the deposition of fibrin and platelets, leading to serious damage to the transplanted kidney and its loss[11]. This form of CsA toxicity has the potential to increase the risk of vascular rejection and thromboembolic complications[12]. Although not proven, it is believed that these effects of CsA are caused by increased thromboxane formation or reduced prostacyclin production, leading to the deposition of fibrin and platelets in blood vessels and their thickening.

Effects of cyclosporine on blood pressure

The use of CsA causes the development of hypertension, regardless of whether it involves patients with transplanted kidneys or autoimmune diseases[13]. However, studying the role of CsA in the development of hypertension is challenging because numerous factors influence its occurrence in patients receiving CsA. The impact of rejection reactions and the function of the transplanted kidney, as well as native kidney disease, renal artery stenosis, or corticosteroids, are just a few risk factors for the development of hypertension after transplantation[14]. Despite the administration of cyclosporine, there is an improvement in the regulation of hypertension after kidney transplantation, which correlates with the improvement of renal blood flow[15].

As CsA causes an increase in renovascular resistance, medications from the group of calcium antagonists are the primary option for treating hypertension after transplantation. Patients on CsA who develop hypertension exhibit reduced peripheral renin activity, leading to an increase in extracellular volume, further contributing to the onset of hypertension. Consequently, diuretics that reduce extracellular volume play a significant role in treating hypertension in these patients[16]. Hypertension associated with CsA usage can also result from impaired pressure natriuresis due to vascular changes caused by CsA.

Cyclosporine nephrotoxicity

Within a year of heart transplantation, there is a significant decrease in the Glomerular Filtration Rate (GFR) in patients who received CsA. However, from the second to the fourth year post-transplantation, only a negligible decrease in GFR is observed. This decline in kidney function in heart transplant patients is believed to be a result of the high doses of CsA administered in the early post-transplant period[17]. The use of newer CsA dosing protocols has been shown to prevent such a decline in GFR. Five-year analyses from numerous transplant centers indicate that CsA administration ensures stable kidney function and graft survival[18]. Data from the United Network for Organ Sharing (UNOS) in the United States, covering the period from 1998 to 2007 and involving a large number of patients treated with CsA, show one-year survival rates of 96.6% and 91.6% for kidney transplantation from a living related donor and a brain-dead donor, respectively. This has led to consideration about whether chronic cyclosporine nephrotoxicity truly exists[19].

Whether cyclosporine nephrotoxicity is dose-dependent is still a matter of debate. Determining the concentration of CsA in the blood after solid organ transplantation is crucial due to the proven correlation between low CsA levels and the risk of acute rejection, as well as the risk of nephrotoxicity in the case of high CsA concentrations in the blood[20, 21]. However, there are significant overlaps between two diametrically opposite options, making it challenging for physicians to establish an accurate diagnosis, especially in the absence of an ideal CsA blood level. One reason for this is the pharmacokinetics of CsA, but the influence of individual variations in sensitivity to CsA must not be overlooked[4].

High doses of CsA are effective and selective inhibitors of T lymphocyte activation, with minimal impact on already activated cytotoxic CD8+ T cells, granulocytes, and

macrophages. This represents a significant advancement and advantage compared to other immunosuppressive drugs. At the same time, CsA does not influence on phagocytes, nor does it have a suppressive effect on bone marrow[22].

The adverse effects of cyclosporine include, in addition to nephrotoxicity, neurological side effects such as headaches, encephalopathy, anxiety, and seizures. It also leads to metabolic and endocrinological disorders such as dyslipidemia, hypomagnesemia, hyperkalemia, gynecomastia, and hirsutism. Additionally, it can cause hypertension, arrhythmias, hepatotoxicity, and diarrhea. However, these adverse reactions are associated with high doses of CsA, reaching up to 25 mg per kilogram of body weight daily. This has led to a change in approach, specifically a reduction in the dosage of this medication in subsequent periods[23].

Administration of low-dose cyclosporine

In the early period of introducing CsA into clinical practice, the initial dose for solid organ transplantation was around 20 mg/kg per day, followed by a gradual reduction every week to 5-10 mg/kg per day. In the case of autoimmune diseases, the dose ranged from 4 to 6 mg/kg per day. Patients undergoing allogeneic hematopoietic stem cell transplantation were typically given lower doses of CsA, usually around 1 mg/kg per day, with a target blood level of 150 to 400 ng/mL[24].

CsA doses less than 3 mg/kg per day are considered low doses, while doses above 4 mg/kg are already considered high doses. The initial attempts to reduce CsA dosage were driven by the desire to decrease/eliminate adverse effects while maintaining immunosuppressive efficacy. However, CsA nephrotoxicity correlates not only with the dose but also with the duration of therapy. If the dose is reduced or CsA is discontinued in a promptly, nephrotoxicity is reversible[25].

Pathophysiology of CsA nephrotoxicity

Acute nephrotoxicity is caused by vasoconstriction of the afferent arteriole, resulting in a decrease in renal blood flow and an increase in vascular resistance in the kidneys. This conclusion is based on experimental studies with high doses of CsA (20 mg/kg). It is believed that these changes are caused by the activation of the sympathetic nervous system and an increase in plasma renin activity[26]. In addition to activating the renin-angiotensin system, CsA increases the concentration of vasoconstrictors such as endothelin and thromboxane while reducing the production of vasodilators such as prostacyclin, nitric oxide, and prostaglandin E2[27]. CsA can induce vasoconstriction by reducing the expression of cyclooxygenase-2 and subsequently decreasing the production of arachidonic acid metabolites[28].

Chronic nephrotoxicity has been recognized since the early use of CsA. Almost 40 years ago, Myers and colleagues published a study on chronic CsA nephrotoxicity analyzing heart transplant patients receiving CsA[17]. Subsequently, deterioration in kidney function with a histological pattern of striped interstitial fibrosis, tubular atrophy, and focal glomerular sclerosis during prolonged use of this medication has been documented in patients with lung and liver transplants, as well as those with autoimmune diseases[29, 30].

Pathohistology of nephropathy caused by ciclosporin

Hyalinosis of arterioles is a typical histopathological finding in cyclosporine nephrotoxicity, characterized by nodular hyaline and deposits in the *tunica media* of the afferent arterioles. One of the commonly described findings is the so-called striped interstitial fibrosis. The resulting ischemia, or tissue hypoxia, leads to damage similar to reperfusion injury, where free oxygen radicals play a key role in cell damage and apoptosis. CsA stimulates the expression of TGF-β, which promotes fibrosis through increased production of extracellular matrix proteins and induction of epithelial-mesenchymal transition[12, 29]. Additionally, the activation of the Renin-Angiotensin-Aldosterone System (RAAS) is crucial for the development of cyclosporine nephrotoxicity, exhibiting vasoconstrictive, proinflammatory, and profibrotic effects[31, 32].

Protocols with reduced doses or with the exclusion of CsA

Considering the evident problem with the nephrotoxicity of CsA, or calcineurin inhibitors, numerous studies have been conducted to assess the effectiveness of protocols with low doses of CsA or tacrolimus. One of the most significant studies is the ELITE-SYMPHONY study, which demonstrated that patients receiving low doses of tacrolimus had better eGFR, the best allograft survival, and the lowest frequency of acute rejections. Slightly weaker but comparable results were observed in the group of patients receiving low doses of CsA[33]. Similar results were obtained in the CAESAR study, which showed that discontinuation of CsA therapy leads to a significantly higher frequency of acute rejections. Additionally, the use of low doses of CsA within immunosuppressive protocols involving mycophenolic acid preparations and corticosteroids demonstrated good efficacy in terms of allograft function and the frequency of acute rejections[34]. Moreover, these studies indicated that reducing CsA dosage or discontinuing its use does not lead to an improvement in the long-term survival of the allograft[35].

While acute CsA nephrotoxicity is supported by numerous scientific evidence, the concept of chronic CsA nephropathy is still a subject of debate, especially after several studies questioned the existence of this entity. Firstly,

histological changes described as characteristic of chronic calcineurin nephrotoxicity are nonspecific. Arteriolar hyalinosis can be present due to pre-existing vascular hyalinosis in the donor, aging, hypertension, and diabetes, as well as findings of glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The presence of tubular microcalcifications can also be seen in ischemic tubular damage, proteinuria, and acute tubular necrosis. Moreover, most of these histological changes are characteristic of recurrent primary kidney diseases[32]. Additionally, Burke and colleagues analyzed 1,663 kidney transplant patients and showed no correlation between CsA levels and changes in creatinine concentration and the frequency of acute rejection episodes. Furthermore, the authors do not associate the development of progressive nephropathy with CsA use and conclude that graft loss is most commonly a consequence of acute rejection and chronic graft nephropathy[36].

The DeKAF study, involving 173 patients with late dysfunction of the transplanted kidney who underwent graft biopsies, made a significant contribution to clarifying the debated issues related to chronic calcineurin nephrotoxicity. The study's results demonstrated that antibody-mediated rejection is very common among patients experiencing late allograft dysfunction, and C4d-positive staining is the most significant risk factor for graft loss. Interestingly, the diagnosis of calcineurin nephrotoxicity did not influence late kidney transplant failure[37].

Based on the mentioned studies, when CsA is administered in high doses, it unquestionably leads to acute nephrotoxicity. However, reduced doses that are adequate for preventing acute rejection do not have harmful effects. At the same time, the concept of chronic CsA nephrotoxicity cannot be conclusively proven. Therefore, the use of this drug continues to play a significant role in solid organ transplantation and the treatment of various other diseases.

Other indications for CsA administration

In addition to its use after solid organ transplantation, CsA is also employed in other indications, such as primary and secondary glomerulonephritis, psoriasis, rheumatoid arthritis, and dry eye syndrome. Because of this, new formulations of this drug with different routes of administration have been developed to the avoid systemic and nephrotoxic effects of CsA.

Steroid-resistant nephrotic syndrome in children is associated with significant morbidity and mortality. However, the use of CsA allows achieving remission in more than half of these highly complicated patients. Treatment must be individualized based on clinical presentation and histopathological findings. CsA is crucial in these patients not only for achieving remission but also because it enables minimizing or excluding corticosteroids from the therapy, which have numerous side effects in children, as well as avoiding cytotoxic drugs and their complications[38].

The treatment of lupus nephritis, especially the choice of maintenance therapy, poses a significant challenge. Although corticosteroids and cytotoxic drugs have been proven effective, their long-term use is associated with serious complications, sometimes life-threatening. Numerous studies have shown that CsA can adequately replace cytotoxic drugs and enable a reduction in the dose of corticosteroids as maintenance therapy. Additionally, there is evidence that CsA is effective in reducing clinical and histopathological manifestations of lupus nephritis, even in patients who have not responded to corticosteroids and cytotoxic drugs. CsA is effective in reducing proteinuria, both in proliferative forms and membranous lupus nephritis[39, 40].

In the treatment of inflammatory bowel diseases, cyclosporin is a new therapeutic option for severe and refractory forms of ulcerative colitis, with the doses used rarely causing nephrotoxic effects. Patients with severe relapses of ulcerative colitis had, until recently, the option of treatment with steroids. If they were resistant to this therapy, colectomy was the next step. Thanks to CsA, which is effective in treating steroid-resistant relapses of ulcerative colitis, the frequency of colectomies has significantly decreased[41].

The treatment of psoriasis with cyclosporin is based on research and conclusions from the medical board of the National Psoriasis Foundation in America. This board, along with its working group, analyzed therapeutic options based on CsA for treating psoriasis, aiming to clearly define its role in the treatment of this disease. The working group concluded that CsA is generally a safe and effective medication for treating psoriasis, particularly useful for treating psoriatic crises, psoriasis that has not responded to initial therapy, and as a transitional option before starting another therapy. Adequate patient selection and careful monitoring of CsA doses and levels will ensure a significant reduction in unwanted effects of CsA in these patients[42].

Conclusion

Since its first application in the late 1970s and early 1980s, CsA has undoubtedly revolutionized transplant medicine by reducing the frequency of acute rejections and improving one-year survival rates for transplanted kidneys. Despite the dose-dependent acute nephrotoxicity, which has become less common with the use of lower CsA doses, and the increasing doubts about the existence of chronic CsA nephrotoxicity, this drug continues to be a cornerstone in therapeutic protocols after solid organ transplantation. Non-immunological adverse effects of calcineurin inhibitors necessitate further research to find optimal immunosuppressive protocols that will provide minimal side effects while maintaining a low risk of acute rejection.

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