Cyclosporine

A review article

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Contents

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Cyclosporine is commonly used as an immunosuppressive agent in organ transplanted and bone marrow transplanted patients worldwide (Wiesner, 1998;Walter et al., 2000;Somech and Doyle, 2007;Adhikary et al., 2008).

History of cyclosporine

Its discovery took place in the Sandoz Laboratory in Basel, Switzerland in January 1972.

For many years there had been a profound need to reduce or eliminate the cytotoxic effects of immunosuppressive agents at that time. The main goal for development of a new agent was to successfully transplant a solid organ taken from a deceased individual into a patient with a failing organ system. Methotrexate, cyclophosphamide, and 6-mercaptopurine (6-MP) had been tried as immunosuppressive agents, but showed high rejection rates, significant toxicities, and poor graft survival in both animal models and human trials. The novel immunosuppressant Cyclosporine A (CyA), with its ability to suppress the immune system without affecting other cells significantly, made a revolution in organ transplantation in the 70's.

The principal discoverers were a team of scientists within different fields of medicine, lead by two Swiss researchers named Jean F. Borel and Hartmann F. Stähelin. It involved a screening program with the antitumor agent ovacilin. Samples from the soil of different locations around the world were collected, and the microorganisms from the soil were tested for anti-fungal and anti-bacterial activity.

The successful result from this screening program was largely contributed by the revelation of metabolites from a new strain of *fungi imperfecti*, found in soil from Wisconsin in the United States and Hardangervidda in Norway (Stiller, 1999;Langone and Helderman, 2004;Rezzani, 2004). Extracted metabolites from the fungal mycelia were called cyclosporine, because they were cyclic compounds found in spores. Later, nearly 30 variations of naturally extracted cyclosporines have been revealed (Langone and Helderman, 2004). All of these have a chemical structure of 11 amino acids and mostly differ from one another by only one single amino acid locus.

Sandoz laboratory put effort into making a potent immunosuppressive agent by researching both the natural derivatives and some newly developed synthetic derivatives of Cyclosporine A. Although the researchers pursued to both find a more potent and less nephrotoxic variant of cyclosporine. Among the compounds tested, the earliest version, namely Cyclosporin A, which proved to be the most potent. The less nephrotoxic Cyclosporin G was thought to be a decent alternative, but was found inferior in suppressing the immune system (Langone and Helderman, 2004). In 1976, Jean F. Borel concluded that their new discovery was efficient in both suppressing the antibody- and cell-mediated immune response (Borel et al., 1994;Langone and Helderman, 2004). Lack of bone marrow suppression was part of the conclusion as well. The elimination of anemia, leukopenia and thrombocytopenia as adverse effects made cyclosporine an interesting subject for further testing.

Dr Roy Calne et al. in Cambridge made a case series in 1978 describing cyclosporine as a potent immunosuppressant, which led to a large demand for cyclosporine to be produced (Calne et al., 1979;Langone and Helderman, 2004). However, after the research group had performed enough transplants, they published an article describing several potential deleterious adverse effects of cyclosporine. The results

from the trials revealed high rates of lymphomas and mortality (Calne et al., 1979). The nephrotoxic adverse effect of cyclosporine was explained by Calne et al. as graft dysfunction and was believed to be caused by acute rejection of transplanted kidneys. Thus the nephrotoxic effects of cyclosporine were not recognized until later.

After the new immunosuppressive agent was recognized and made known, a need to study its biochemical actions presented itself. Another goal was to develop ways to increase the efficiency of intestinal absorption. Although the cyclosporine was extracted for the first time in 1972, it wasn't commercially available until 1983 when Sandimmune® was released. It was first only available as a liquid concoction depending on the patient's bile to be absorbed. This, as well as splitting into 12-hour doses, would eliminate some of the difficulties related to oral absorption. One of the main targets was to keep the serum levels as constant as possible in order to avoid neurological adverse effects as serum concentration of Cyclosporine A [CyA] peaked.

The availability of cyclosporine as a virtually unchallenged immunosuppressant in transplantation medicine had been going on for many years since its discovery. In fact, it wasn't until 1997 when a macrocyclic lactone derived from actinomyces was found, that cyclosporine would finally meet serious competition. This new calcineurin inhibitor was named tacrolimus, commercially known as Prograf®(Langone and Helderman, 2004). Several studies comparing the immunosuppressive effects and adverse effect profiles of tacrolimus and cyclosporine, conclude that tacrolimus significantly reduces the risks of death after liver transplantation, graft loss, acute rejection and steroid-resistant rejection (Haddad et al., 2006;McAlister et al., 2006). According to many clinical studies, tacrolimus also increases the risk of new-onset diabetes. Differences between tacrolimus and cyclosporine will be discussed in detail later.

Therapeutic effects

The biochemical effect of calcineurin inhibitors, such as cyclosporine and tacrolimus, is ultimately the inhibition of T-cell activation (Smith et al., 2003;Taylor et al., 2005). The underlying mechanism for this is the blocking of Ca^{2+} activation of calcineurin when the T-cell is stimulated by antigen. Binding of foreign antigen to receptors on the T-cell surface leads to several signalling pathways, which in turn increase intracellular calcium concentration [Ca^{2+}]. Increased [Ca^{2+}] activates calmodulin and calcineurin B, which then activate the catalytic subunit of calcineurin called calcineurin A. This phosphatase dephosphorylates the nuclear factor of activated T-cell (NF-AT) and permits the NF-AT to enter the nucleus. By altering the expression of genes specific for T-cells, it influences synthesis and release of interleukin-2 (IL-2), which is a regulator of T-cell proliferation and differentiation. IL-2 has both autocrine and paracrine actions on T-cells. The inhibition of the calcineurin complex also counteracts the release of T-cell–derived lymphokines, including IL-2, IL-3, IL-4 and gamma interferon This in turn inhibits the clonal expansion of helper and cytotoxic T-cells. In order to bind to calcineurin, cyclosporine is first bound to cyclophilin in the cytosol. The principal antagonistic action of cyclosporine is binding to the catalytic subunit of the calcineurin complex, leading to decreased dephosphorylation of NF-AT, and over the last steps decreasing T-cell proliferation and growth. Tacrolimus (FK-506) on the other hand, interacts with FK-506 binding protein (FKBP) before binding to the calcineurin subunit.

Interactions and adverse effects

Even though cyclosporine and tacrolimus ultimately have the same mechanism of action, several studies have concluded that they only to a certain degree share the same profile of adverse effects (Paul, 2001;Smith et al., 2003). Smith et al. have described that both agents are acutely and cronically nephrotoxic and causes hyperkalemia and hypomagnesemia to a similar degree. The same group also concludes that cyclosporine tends to cause hyperlipidemia, hypertension, gingival hyperplasia and hypertrichosis more frequently compared to tacrolimus. The latter on the other hand, tends to have more neurological and gastrointestinal adverse effects than cyclosporine, in addition to an increased risk of hyperglycemia. Careful monitoring of serum concentrations is important because of a narrow therapeutic window for both agents, as well as known interactions with several other drugs. Interference with cytochrome P450 3A4 (CYP3A4), a member of the cytochrome P450 mixed-function oxidase system, is the main problem. Drugs such as rifampine, Phenobarbital, phenytoine, nafcilline and carbamazepine all decrease serum [CyA] and [FK506] by inducing CYP-3A4, while macrolides, antifungal agents and some calcium inhibitors such as verapamil increase serum concentrations by inhibiting CYP3A4. It is also important to warn patients against intake of grapefruit or grapefruit juice along with cyclosporine, as it is known to inhibit CYP3A4.

The therapeutic effects of cyclosporine are relatively well-known. However, it has been found a clear connection between cyclosporine use and vasoconstriction in multiple organs. One of the most common adverse effects of cyclosporine use is its effects leading to nephrotoxicity. Clinical and experimental trials have shown that a supratherapeutic dose of CyA may lead to reduced kidney function. It is believed that cyclosporine-induced constriction of the afferent arteries to the kidneys is causing an

altered renal circulation. This is also confirmed by studies showing reduced renal blood flow and glomerular filtration rate with calcineurin inhibitor treatment. The mechanisms of this might be an imbalance between concentrations of the constricting thromboxane A2 and the dilating prostaglandin E2 (Butterly et al., 2000;Olyaei et al., 2001). It has also been shown that CyA may activate the sympathetic nervous system, leading to increased systemic vasoconstriction. Some studies have concluded that CyA enhances the release of endothelin-1, constricting the vessels even further (Butterly et al., 2000;Prevot et al., 2000;Wilasrusmee et al., 2003). The role of nitric oxide (NO) is another hypothesis. NO is known to be an important regulator of renal vascular tone, and CyA is thought to be interfering with the production of NO.

Although the nephropathy is reversible in short-term CyA treatment, a prolonged cyclosporine-induced vasoconstriction may lead to acute tubular sclerosis and irreversible lesions in the tubular interstitium (Olyaei et al., 2001). Finally, this may cause chronic and irreversible nephrotoxicity.

The connection between diabetes mellitus and the use of calcineurin inhibitors is well documented (Smith et al., 2003;Rezzani, 2004;Guerra et al., 2007;Vincenti et al., 2007). In the case of CyA, insulin production and secretion is inhibited, while the volume of ß-cells in the Islets of Langerhans is decreased(Rezzani, 2004). Some trials show that organ transplanted patients with tacrolimus treatment have a higher risk of hyperglycaemia and diabetes mellitus than respective patients undergoing CyA treatment (Smith et al., 2003;Rezzani, 2004;Guerra et al., 2007;Vincenti et al., 2007).

Hypertension is a common adverse effect caused by cyclosporine A use. Systemic vasoconstriction leading to hypertension within only a few days of cyclosporine

administration has been documented. A typical characteristic of this hypertension is the lack or reversal of nocturnal fall in systemic blood pressure. This has lead to symptoms like nocturnal headache and increased nocturnal urination. An altered circadian rhythm is thought to be the culprit of these symptoms. In some studies, some of the patients developed retinal hemorrhages and central nervous symptoms in addition to left ventricular hypertrophy, lacunar strokes and microalbuminuria (Ventura et al., 1997;Rezzani, 2004).

CyA treatment is associated with an increased risk of hyperlipidemia, i.e. increased levels of LDL-cholesterol and triglyserides. Studies have concluded that the risk is higher in CyA treatment compared with tacrolimus, and some trials have shown a decrease in blood lipids after conversion from CyA to tacrolimus. In the same trials, the systemic blood pressure was higher during administration of CyA compared with that of tacrolimus (Calne et al., 1998;Paul, 2001;Guerra et al., 2007;Vincenti et al., 2007).

Seizure is one known neurological adverse effect of CyA use. It may be influenced by associated factors such as fluid retention, hypertension, high-dose steroids, graft dysfunction and demyelination. Hypomagnesaemia, which can be caused by CyA itself, might be a contributor as well, but some trials show that some patients had seizures although their magnesium levels were within normal range. Multiple other neurological complications of CyA use include neuralgia, paresthesia, confusion, hemiplegia, tremor, occipital seizures, ataxia and transient cortical blindness (Rezzani, 2004).

Clinical use and efficacy of calcineurin inhibitors

- Liver transplantation

Several studies have described the efficacy of cyclosporine and tacrolimus in liver graft survival (Pichlmayr et al., 1997;Wiesner, 1998;O'Grady et al., 2002). A randomised study involving 529 patients compared graft survival with the administration of tacrolimus combined with steroids and CyA combined with aziathropine and steroids (Pichlmayr et al., 1997). The incidence of acute, recurrent acute, and chronic rejection after 3 years post-transplant, were substantially lower among the patients receiving tacrolimus, but the graft and patient survival were at the same level. Another trial with the same amount of patients undergoing post-transplant treatment, concluded that the incidence of acute rejection was significantly lower in the tacrolimus treated group 5 years post-transplant, although the incidence beyond the first year of immunosuppressive therapy was similar (Wiesner, 1998). Graft and patient survival after 5 years was equal.

- Renal transplantation

Several trials comparing the effects of CyA and tacrolimus in immunosuppressive treatment of kidney transplantation have been made with follow-ups after 6 and 24 months. The results were quite similar for both immunosuppressants in graft and patient survival, but with clearly less acute rejection among the patients undergoing treatment with tacrolimus (Pirsch et al., 1997;Ahsan et al., 2001;Margreiter, 2002). Although there are studies concluding the beneficial use of tacrolimus in terms of acute graft rejection, there are no evidence that tacrolimus improves graft survival over a longer period of time. A study executed in Europe examined 451 patients receiving either tacrolimus or CyA combined with steroids and aziathropine (Mayer

et al., 1997). Patient and graft survival rates were similar at 5 years post-transplant, but the chronic rejection rate was substantially lower in tacrolimus treated patients (Mayer, 2002). In this case, the difference was 6.6% for tacrolimus versus 15.3% for cyclosporine. There are evidence that immunosuppressive treatment with tacrolimus is beneficial in some selected subgroups such as patients with delayed function. One trial concluded that graft survival rates are significantly increased in tacrolimus therapy compared with CyA treatment (Gonwa et al., 2003).

- Stem cell transplantation

Two large randomized trials have compared the combination of CyA and methotrexate with tacrolimus and methotrexate in stem cell allograft transplantation (Ratanatharathorn et al., 1998;Nash et al., 2000). Both concluded that the incidence of acute graft-versus-host-disease (GVHD) was clearly lower in patients undergoing tacrolimus treatment, although the difference in chronic GVHD rates after 2 years was marginal. One trial even concluded that tacrolimus administration in stem cell transplantation from siblings had a lower rate of patient survival than treatment with CyA (Ratanatharathorn et al., 1998). The administration of mycophenolate mofetil in combination with CyA has been compared with the standard CyA/metothrexate treatment (Bolwell et al., 2004). The results were similar rates of GVHD for both combinations and comparable rates of overall survival. However, CyA/mycophenolate showed a faster engraftment than CyA/methotrexate in the same trial.

- Cardiac transplantation

Trials have been made in Europe and the United States comparing the efficacy of an oil-based CyA formulation with the combination of tacrolimus, aziathropine and steroids (Taylor et al., 1999;Reichart et al., 2001). Heart graft survival and patient survival rates were comparable one year after transplantation, while tacrolimus proved to induce less hyperlipidemia and hypertension than CyA. Another large study examining a time span of 18 months showed similar results in patient and graft survival but also concluded that recurrent graft survival was slightly lower in tacrolimus-treated patients (Grimm et al., 2006). One unique source of error after heart transplantation was the possible development of coronary allograft vasculopathy (CAV). So far there is no evidence that CyA or tacrolimus reduce the risk of this complication during long-term follow-up (Keogh, 2004). Indirectly however, the beneficial properties of tacrolimus involving hyperlipidemia, glucose metabolism and hypertension might be preferable in patients who develop CAV after cardiac transplantation. The incidence of CAV was increased in patients receiving steroids in combination with both CyA and tacrolimus. As for immunosuppression in liver and renal transplantation, the conclusion for cardiac transplantation was that CyA and tacrolimus have about the same efficacy on patient and graft survival, and the choice of which agent to use depends on the adverse effect profile that suits best for each patient individually.

Case report: Patient undergoing cyclosporine A treatment developed bilateral optic disc swelling.

A heart transplanted patient undergoing CyA treatment for 15 years experienced impairment of the visual field and reduced visual acuity due to bilateral optic disc

swelling. During the preceding 15 years, the patient's vision was normal. After diagnosing optic disc swelling, the patient's CyA administration was substituted by everolimus. His symptoms improved over a time span of 4 months with no further significant improvement after 7 months.

Previous case reports have shown possible ocular adverse effects of CyA, but this case was unusual because of the long time span between start of CyA administration and the onset of signs and symptoms. By comparison, other trials have shown onset of symptoms as early as after 30 and even 12 months of CyA use. To our knowledge, no previous trials concerning heart transplanted patients with cyclosporine-induced optic disc edema are known.

Different studies have shown variation of remission of visual signs and symptoms from 5 days to 8 months after CyA withdrawal (Avery et al., 1991;Cruz et al., 1996). These studies describe the visual adverse effects of CyA as completely reversible. In our case, improvement started 4 months upon cessation of Cya with full remission of the optic disk edema within 7 months. The patient experienced however sequelae of optic disc swelling in form of persistent mild visual field defects and slightly impaired visual acuity.

Causes of optic disc swelling include mass lesions, sinus venous thrombosis, hypertensive papillopathy, diabetic papillopathy, anterior ischemic optic neuropathy (both nonartetitic and arteritic), optic neuritis, uremia and disorders of the parathyroidea. They were all excluded in our patient. Idiopathic intracranial hypertension (pseudotumor cerebri) which might cause bilateral disc edema was discussed, but found unlikely due to lack of typical symptoms related to increased intracranial pressure such as headache, transient visual obscurations, and diplopia.

Neuroimaging (MRI) was normal and lumbar puncture was considered redundant. The medication regimen of the patient was examined. Since the dosage of prednisolone was not changed during the remission of the patient's symptoms in our case, there is no reason to believe that it could be the culprit of his ocular symptoms. In addition to steroids, thiazide could possibly provide ocular symptoms indirectly through electrolyte disturbances. In this case however, blood electrolytes were monitored regularly and showed concentrations within normal range.

Possible effects leading to microvasculopathy

Long-term microangiopathic effects of CyA are well described in the literature, especially in studies involving nephrotoxicity. Many articles relate this to an altered local endothelin-1 (ET-1) activity, as endothelin-1 increases vascular tone and reduces renal glomerular filtration rate (Li et al., 2004). Although endothelin is produced in a wide range of cell types, ET-1 is only found in endothelial cells. When endothelial damage, hypoxia or ischemia occur, ET-1 is rapidly produced and released. ET-1 has also been shown to regulate sodium reabsorption. Finally, effects on sympathetic nerve system have been discussed (Elzinga et al., 2000). One study demonstrated endothelial dysfunction induced by CyA in an in vitro cell culture (Wilasrusmee et al., 2003). The focus is not whether CyA induces vascular contraction, but rather how CyA affects the vascular endothelium. Specifically, CyA induces ET-1 gene expression and release, with mechanisms that are not completely understood. In this study, only ET-1 gene expression proved to induce microangiopathy after several mediators were tested. In addition, it was demonstrated that CyA stimulated endothelial cells to secrete an excessive amount of ET-1.

Another possible interaction with vascular tone in cyclosporine use is its effect on nitric oxide (NO) (Li et al., 2004). CyA may interfere with the production of NO, leading to increased vessel constriction. NO is produced from l-arginine by 3 identified isoforms of NO synthase. The synthesis of the different NO synthase isoforms, and thereby an altered production of NO, has proved to be interfered by chronic CsA use. One study suggested that CyA-induced hypertension is caused by a conversion of NO into peroxynitrites (Calo et al., 2000). It is discussed to be caused by CyA's ability to induce production of superoxides (O2-), causing oxidative stress where NO molecules are destroyed. The breakdown of peroxynitrites creates NO^{3}-/NO^{2}- which are even more highly reactive than superoxides. On the other hand, other studies are inconclusive and suggest that the effects of reduced acetylcholine activity might be the main reason for increased vascular tone rather than a direct effect of CyA treatment in transplanted patients (Bracht et al., 1999;Calo et al., 2000;Calo et al., 2002;Li et al., 2004;Ramzy et al., 2008).

CyA interference with the sympathetic nervous system as a possible cause of microvasculopathy has been discussed in several articles, but the results from these trials are in many cases inconclusive or conflicting. There are evidence that CyA-treated heart-transplanted patients with hypertension have an increase in discharge from sympathetic nerves. Experimental trials show interference with the sympathetic nervous system and increased arterial blood pressure through activation of excitatory neural reflexes. In contrast, opposing studies have shown that CyA inhibits vasodilatation without affecting sympathetic activity. The variety of results from these trials leads to the conclusion that CyA may induce hypertension by impairment of peripheral vasodilation or alteration of vascular mechanisms isolated from sympathetic nervous regulation.(Scherrer et al., 1990;Lyson et al., 1994;Stein et al., 1995;Ventura et al., 1997)

Some of these potential vascular mechanisms include uncoupling of acetylcholine and interference with an endothelial-mediated pathway which regulates the uptake of calcium. CyA has also been demonstrated to induce apoptosis by increasing expression of pro-apoptotic proteins and decreasing expression of the survival gene bcl-2. An upregulated expression of angiotensin II receptors is another possible cause of CyA-mediated vasoconstriction that could also be connected with decreased renal blood flow due to afferent arteriolar constriction. Increased sensitivity to constrictive stimuli has been postulated as well. The cause of is thought to be CyA-induced rise of calsium consentrations in smooth muscle cells. Even though many possible effects of CyA on vessel tone have been suggested and tested, the cause-effect relationships are still to be completely described.(Mason, 1990;Avdonin et al., 1999;Allison, 2000;Serkova and Christians, 2003)

Future aspects of cyclosporine and other immunosuppressive agents.

Since the first days of CyA development, several immunosuppressive agents have become available for clinical use. Tacrolimus has already been mentioned and was released in 1997. Another promising alternative for solid organ transplantation are the relatively newly released macrolides known as mTOR inhibitors. The need for a new immunosuppressive agent with less adverse effects have become clearer after long time use of CyA and tacrolimus. The problem is not only the nephrotoxicity and the risk of developing cardiovascular disease, but also the fact that chronic rejection still remains a major problem. Sirolimus is the most common mTOR inhibitor and has shown promising graft survival rates in solid organ transplantation. Another interesting feature is the synergy of mTOR inhibitors with CyA, tacrolimus, steroids and mycophenolate mofetil. The specific effect of sirolimus on T-cell proliferation resembles that of CyA by inhibiting the IL-2 induced proliferation of T-cells. However, it is fundamentally different because of its inhibition of the mTOR

signalling pathway. Although further studies are required to make conclusions about the efficiacy in solid organ graft survival during sirolimus use, trials have shown that sirolimus gives reduced rates of nephrotoxicity and hypertension compared with CyA. Sirolimus may therefore, either as a monotherapy or in combination with traditional immunosuppressive agents, improve adverse effect profiles among different patient groups (Neuhaus et al., 2001;Langone and Helderman, 2004;Everson, 2006;Levy et al., 2006).

Even if sirolimus may reduce many of the complications seen during CyA treatment, the mTOR inhibitor itself has troublesome adverse effects. The most important ones include metabolic effects, predominantly increased serum blood levels of triglycerides and cholesterol. mTOR inhibitors have also shown to decrease uric acid concentrations as well as to elevate serum liver enzymes. Finally, myelosuppression has been reported, leading to thrombocytopenia, decreased leucocyte count and anaemia. Especially in renal failure or impairment, anaemia spells serious problems which is complicated by the fact that these patients respond less to supplementary erythropoietin (Smith et al., 2003;Taylor et al., 2005).

The future of CyA as an immunosuppressive agent is depending largely on whether or not it's possible to combine CyA with less nephrotoxic agents. It is clear that calcineurin inhibitor-sparing regimens will be strictly preferred in order to reduce nephrotoxicity and increase graft and patient survival in solid organ transplantation. Trials have shown that these non-nephrotoxic regimens allow CyA to be reduced or even eliminated in immunosuppressive therapy. Combinations of sirolimus with CyA and with tacrolimus have been given most attention, and a thorough analysis of efficacy, tolerance and safety of the mTOR inhibitors will show if sirolimus qualify as the new standard immunosuppressant. Should this be the case, it is predicted that sirolimus will revolutionize the immunosuppression of solid organ transplantation in

the same way that CyA did in the 70's. However, the execution of more randomized trials involving large numbers of patients with long-term follow-up is still required (Neuhaus et al., 2001;Taylor et al., 2005;Everson, 2006;Guerra et al., 2007).

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