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Chapter 1

Drug Interactions and Potential Side Effects of Cyclosporine

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Abstract

Since its discovery in Sandoz laboratories in 1972, cyclosporine (CsA) has revolutionized transplant medicine. Initially discovered while searching for novel antifungal agents, CsA was found to have many immunologic properties that made it an attractive compound for immunosuppression. It is currently one of the most important immunosuppressive agents for a wide range of organ transplantations, including kidney, liver, heart, lung, pancreas, and intestine. In its 40 years of life, CsA was shown to be also an effective treatment option in autoimmune and inflammatory diseases, such as rheumatoid arthritis, uveitis, psoriasis, and atopic dermatitis.

CsA is a lipophilic, cyclic peptide with a molecular weight of 1202 Daltons. In plasma, it is 90% protein bound, mostly to lipoproteins, but also to albumin and globulins. In blood it is extensively distributed in erythrocytes. Bioavailability, which was initially characterized by a high interindividual variability, has been significantly increased by the development of a microemulsion formulation, which also greatly reduced the variability. Metabolism is primarily hepatic via the cytochrome P450 system, and CsA metabolites are eliminated mostly in the bile. Coadministration of drugs affecting the cytochrome P450 system is known to modify CsA levels.

The immunosuppressive properties of CsA result from inhibition of calcineurin, a calcium- and calmodulin-dependent phosphatase. Intracellularly, CsA binds to cyclophilin, forming a complex that inhibits, by competitive binding, phosphatase activity of calcineurin. This inhibition then suppresses the transcription of IL-2 and thus T-cell activation, via inhibition of the dephosphorylation and translocation of the nuclear factor of activated T cells (NFAT). CsA was found to inhibit both in vitro cell-mediated

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lysis as well as lymphocyte sensitization by allogeneic target cells. However, calcineurin and NFAT isoforms are not T-cell specific, therefore inhibition of this pathway by CsA not only results in immunosuppression, but gives also rise to toxicity.

The most notable toxic effect is nephrotoxicity, but other reported side effects include, in decreasing order of frequency, hypertension, hypercholesterolemia, hypertrichosis, gingival hyperplasia, uric acid and electrolytes alterations, thrombocytopenia, neoplasms, and diabetes. Nephrotoxicity has gained the most attention over the years. Currently, it is well known that acute and chronic renal damage may be important consequences of CsA therapy, but it is also known that most persistent renal dysfunction is related to prolonged therapy, or doses of greater than 5 mg/kg/day, and may also be related to individual susceptibility. The chance of developing renal impairment during CsA therapy should be minimized by screening patients at baseline for risk factors such as hypertension, advanced age, pre-existing renal conditions, abnormalities in absorption of CsA, and concomitant medications. Furthermore, protocols for the management of CsA-associated hypertension and nephrotoxicity have been developed.

Introduction

Discovered while searching for novel antifungal agents, cyclosporine (CsA) was first isolated from the soil fungus *Tolypocladium inflatum* in 1970 [1]. While its antifungal activity was shown poor, many immunologic properties were found in 1976, in particular a potent immunosuppressive effect that made it a very attractive agent for immunosuppression following solid organ transplants. It was Borel, while performing a series of experiments on cell-mediated immunity with antiinflammatory, immunosuppressant and antimitotic agents, who found that CsA inhibited both in vitro cell-mediated lysis as well as lymphocyte sensitization by allogeneic target cells [2]. Subsequently, a European multicenter trial demonstrated higher one-year graft survival in recipients of cadaveric renal transplants treated with CsA compared to azathioprine and steroids [3]. These promising results opened the way to clinical approval of CsA for use in the early 1980s. With improved rates of acute rejection and one-year graft survival, CsA has become a mainstay for immune suppression of renal and other solid organ transplants, and despite the increased availability of new therapeutic options, CsA is still one of the most widely used and effective immunosuppressants in transplant medicine. Later on in its development story, CsA was shown to be also an effective treatment option in autoimmune and inflammatory diseases, such as rheumatoid arthritis, uveitis, psoriasis, and atopic dermatitis [4-8]. Currently, CsA is one of the most frequently used systemic agent for the treatments of psoriasis and atopic dermatitis worldwide.

CsA adverse effects are nowadays well-known, especially nephrotoxicity and metabolic abnormalities, but are for the most part, dose dependent and related to duration of therapy.

This article provides a comprehensive review of the mechanism of action, pharmacokinetics, potential drug interactions and adverse effects of CsA.

Mechanism of Action of CsA

CsA is a cyclic endecapeptide (Fig. 1) with a molecular weight of 1202 Daltons [9], which acts directly on cells of the immune system, primarily T cells, and targets the major effector pathways of immune-mediated response and inflammation. These effects explain its efficacy both in the prevention of transplant rejection and in immune-mediated dermatoses [10].

Calcineurin is a calcium/calmodulin-dependent serine threonine protein phosphatase. Activated calcineurin dephosphorylates regulatory sites on several transcription factors, most notably nuclear factor of activated T-lymphocytes [NFATs]. CsA inhibits calcineurin by forming an intracellular complex with cyclophilin. This step prevents the dephosphorylation of NFATs and its subsequent translocation from the cytoplasm to the nucleus in an IL-2-mediated process [11-13]. The final result is the inhibition of the transcription of genes encoding interleukin-2 [IL-2], which is necessary for the full activation of the T-cell pathway, interferon gamma, and granulocyte-macrophage colony stimulating factor (GM-CSF) [9,11,12]. Therefore, CsA decreases epidermal and dermal lymphocytes and macrophages and inhibits the activation of T cells, natural killer cells, and antigen-presenting cells [14]. CSA also inhibits keratinocyte hyperproliferation, histamine and prostaglandins release from mast cells, and downregulates the expression of cellular adhesion molecules on dermal capillary endothelium [15,16].

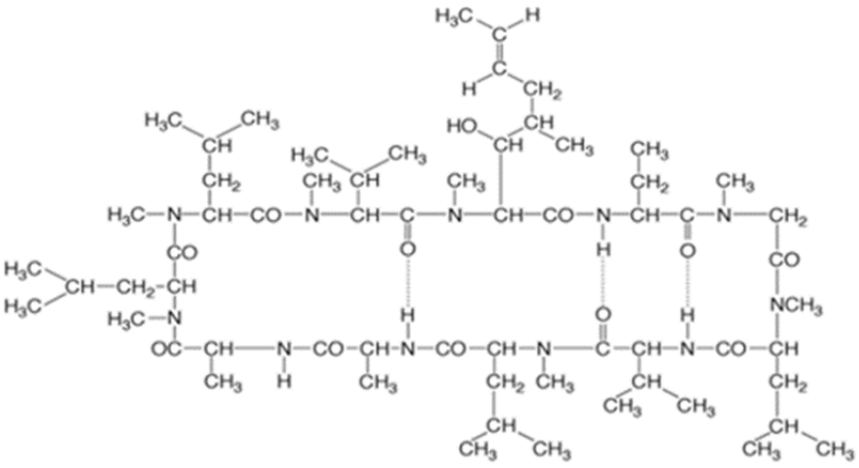

Figure 1. Structure of cyclosporine.

Pharmacokinetics of CsA

Absorption

CsA is a lipophilic molecule that is poorly absorbed when administered orally. Absorption occurs within approximately 30 minutes, and peak serum concentration (C_{max}) is observed 2 to 4 hours after the dose [17-19]. The original orally administered formulation of

CsA (Sandimmun, Novartis) showed wide variations in inter- and intrapatient bioavailability, ranging from 1% and 89% [17, 20, 21]. Because of this great variability in absorption, a more hydrophilic microemulsion formulation (Neoral, Novartis) was developed. Kovarik et al. demonstrated a more stable concentration-time profile and bioequivalent peak-trough fluctuation in both fasting daytime and nonfasting nighttime administration of the microemulsion formulation when compared to that of the commercially available formulation. Furthermore, there was a 30% increase in AUC in the microemulsion formulation due primarily to absorption-related pharmacokinetic differences [22]. The new formulation was approved by the FDA for the prevention of transplant rejection in 1995 and for the treatment of rheumatoid arthritis and psoriasis in 1997. The results of a randomized, double-blind study comparing the two formulations showed that the microemulsion provides a more rapid response, higher remission rates in the first 8 weeks, and a 10% lower dose to maintain efficacy than the original formulation [23]. Other studies demonstrated the pharmacokinetic consistency of the microemulsion formulation and the differences with the original formulation [20,22]. A metanalysis of all available data on the bioavailability of Sandimmun® and Sandimmun Neoral® concluded that the two formulations are not bioequivalent, so they should be used as independent therapeutic approaches for immunosuppression and any switching requires particular caution [24]. The therapeutic window of CsA is narrow both in terms of therapeutic efficacy and of drug toxicity [22]. Further, there is currently significant variability in the pharmacokinetics of newer generic forms of the microemulsion formulation of CsA [25, 26]. Thus, different brands should not be used interchangeably without strict supervision to avoid alterations in CsA concentration resulting in a lower efficacy or increased toxicity of the drug. Accordingly, it is recommended that the brand be specified with each prescription [27].

Distribution

Due to its lipophilicity, CsA is widely distributed throughout the body. In plasma, it is 90% protein bound, mostly to lipoproteins but also to albumin and globulins, and is easily transferred between different proteins [17]. In blood, CsA is extensively distributed in erythrocytes. Several factors may affect CsA blood levels and consequently its clinical efficacy. Since CsA is highly lipophilic, a high dietary fat intake can affect its serum concentrations related to increased serum lipid levels [28]. A higher serum concentration of CsA is obtained if the drug is administered before meals [17, 29], potentially allowing the daily dose of CsA to be reduced when compared with postprandial administration. CsA has been reported to have a first-pass effect of 27% in the liver [30]. Its biphasic distribution is thought to be due by the enterohepatic recirculation of the drug from the bile to the small intestine [17].

Metabolism

Metabolism is primarily hepatic by the cytochrome P450 system, mainly CYP3A4, and CYP3A5. CsA metabolism is also controlled by the efflux p-glycoprotein pump (PGP), a transmembrane transporter, which is expressed in the gastrointestinal tract and liver and

encoded for by the multidrug resistance-1 gene (MDR1, also known as adenosine triphosphate-binding cassette B1 [ABCB1]) [31-38]. Many single-nucleotide polymorphisms in the genes encoding CYP3A4, CYP3A5, and PGP have been identified and are thought, at least in part, to account for the variability in pharmacokinetics of cyclosporine.

Elimination

CsA elimination follows first-order kinetics with a constant fraction of drug eliminated per unit time [17]. Metabolites of CsA are excreted primarily in the bile. Only 5-6% of the dose is excreted in urine, mainly as CsA metabolites, with 0.1% of the dose excreted unchanged [17]. The elimination half-life of CsA in serum is between 6 and 24 hours [17, 19].

Pharmacokinetics in Children

It has to be taken into account that CsA pharmacokinetics are altered in children, with clearance rates of up to four times that of adults over 40 years of age, resulting in lower blood concentrations for the same dose (39, 40). Mochon et al have demonstrated important features of CsA pharmacokinetics in children: first, a consistent diurnal variation in morning and evening trough levels and a shorter t_{max}, reflecting potential differences between children and adults in gastrointestinal absorption of CsA; second, significant differences in apparent steady-state volume of distribution and blood clearance, with the youngest children (2-5 years) exhibiting more rapid drug clearance than those aged > 10 years and thus requiring higher doses of CsA [41]. The clearance of CsA after intravenous administration does not appear to be related to age [42]. It has been hypothesized that the decreased bioavailability is related to shorter bowel length in children, rather than to metabolic differences [43].

Pharmacokinetics in Obese Patients

CsA is dosed on a weight per weight basis and clinical observations have suggested that in obese patients the distribution of the drug is limited primarily to lean body mass, thus leading to potential toxicity if patients are dosed according to their actual body weight [44, 45]. No significant differences in bioavailability, elimination half-life, clearance, and steady-state volume of distribution of the drug were observed when calculations were normalized by ideal body weight. When administered doses based on actual body weight, obese transplant recipients showed a mean serum trough level almost double that of non-obese recipients [46]. Trough levels of cyclosporine have also been shown to increase with the obesity index, with a resulting increase in nephrotoxicity [47. Therefore, it is generally recommended to calculate the required CsA dose on the basis of the patient's ideal body weight rather than actual body weight, in order to limit the risk of adverse effects. The maintenance dose is then established as the lowest effective dose to achieve disease control.

Drug Interactions

With CsA widespread use, many drug interactions have been identified. In general, coadministration of interactive drugs should be avoided whenever possible, however, if it cannot be avoided, careful CsA therapeutic monitoring and modification of dosages accordingly are necessary to avoid therapeutic failure or toxicity. CsA interactions may be caused by alterations of the pharmacokinetic parameters and/or alterations of physiologic or pharmacologic effect. Potential sites of interaction include the intestine, lipoproteins, the liver and the kidneys [48].

Pharmacokinetic Interactions

Pharmacokinetic interactions are those which produce alterations in the absorption, distribution, metabolism, and elimination of CsA.

Absorption

CsA absorption from the gastrointestinal tract is slow and incomplete. Administration with food and concurrent administration of other drugs influence the absorption and bioavailability of CsA [48].

Distribution

Patients undergoing transplantation may require parenteral nutritional support, including intravenous fat emulsions, and CsA is a highly lipophilic compound, known to bind with serum lipoproteins, thus CsA levels should be closely monitored in patients receiving intralipid therapy.

Metabolism/Elimination

As reported before, CsA is almost entirely metabolized by the cytochrome P450 3A system. Therefore, drugs that inhibit or stimulate the cytochrome P450 system increase or decrease CsA levels respectively (Tables 1 and 2) [49, 50]. CsA can delay the metabolism of multiple agents, including digoxin, prednisolone, diclofenac, and methotrexate, leading to increased concentration and toxicity of these drugs. Special attention has been paid to CsA interactions with statins. Dyslipidemia is frequent in patients with renal failure and in transplant recipient patients. This leads to a wide use of statins in patients treated with CsA as post-transplantation immunosuppressive therapy and drug–drug interactions are likely to occur. Statins that are metabolized by CYP3A4 enzyme system, like atorvastatin, should be avoided because of their high risk for drug–drug interaction with CsA that may result in severe toxicity. Pravastatin may interact with CsA in a different way since it has been shown to be actively transported in the liver and the kidney by specific transport proteins that may either be involved in CsA elimination or inhibited by CsA. At the same time, it has been shown that fluvastatin is not a substrate of these transporters and that it penetrates the cells only by simple diffusion. As a result, it seems that fluvastatin is less likely to interact with CsA in transplant recipients patients and that it should be the statin of choice in such patients

[51]. Moreover, lovastatin, when administered concomitantly with CsA was associated with a 30% increase in the occurrence of a rare event such as rhabdomyolysis [52].

Heavy alcohol intake can also increase cyclosporine levels [53]. In the acute setting, ethanol is metabolized preferentially by the liver resulting in an 80-85% reduction in metabolism of other substrates, such as drugs. An acute rise in CsA level has been reported following alcohol binge drinking, while no effect was observed in renal transplant recipients following ingestion of a single dose of ethanol [53].

Table 1. Drugs that increase cyclosporine plasma concentrations*

Calcium channel blockers (diltiazem, nicardipine, verapamil, and mibefradil)
Antifungals (fluconazole, itraconazole, ketoconazole, and voriconazole)
Macrolide antibiotics (erythromycin, clarithromycin, and josamycin)
Doxycycline
Gentamicin and tobramycin
Ticarcillin
Ciprofloxacin
Oral contraceptives and androgen steroids
Allopurinol
Bromocriptine
Amiodarone
Ranitidine and cimetidine
Metoclopramide
Methylprednisolone
Protease inhibitors
Statins (especially atorvastatin and simvastatin)
Danazol
Thiazide diuretics
Furosemide
Warfarin

* by inhibiting the cytochrome P450 system

Table 2. Drugs that lower CsA plasma concentrations*

Anticonvulsants (carbamazepine, phenobarbitone, phenytoin, and valproate)
Rifampicin
Rifabutin
Isoniazid
Octreotide
Orlistat
Terbenafine
Sulfinpyrazone
Probucol
Troglitazone
Ticlopidine
Metamizole
Selective serotonin reuptake inhibitors (sertraline)
Nafcillin
St John's Wort (Hypericum perforatum)

*by stimulating the cytochrome P450 system

Pharmacologic/Pharmacodynamics Interactions

Nephrotoxic drugs can impair renal function during cyclosporine treatment and should be avoided whenever possible (Table 3).

Table 3. Drugs that may increase the risk of CsA-associated nephrotoxicity

Aminoglycosides
Melfalan
Diclofenac
Amphotericin B
Ketoconazole
Trimetoprim (with or without sulphametoxazole)
Fluoroquinilones
Acyclovir
Cidofovir
Foscarnet
Cimetidine, ranitidine
Tacrolimus
Colquicine
NSAIDs
Analgesics
Contrast media
Fibrates

CsA Potential Adverse Effects

In addition to its effects on immune function, CsA possesses several adverse effects. The most notable is nephrotoxicity, but hypertension, hyperlipidemia, gingival hyperplasia, hyperkalemia, neurotoxicity, hypomagnesaemia, hyperuricemia, thrombotic microangiopathy are also reported (54). Other clinical undesirable manifestations of CsA treatment include tremor, paresthesia, muscle cramps, myalgia, hirsutism, anorexia, nausea, vomiting and abdominal pain (Table 4). For the most part, these side effects are dose-dependent, related to the duration of therapy, and reversible on discontinuation, although in some cases structural renal abnormalities may be persistent [48, 55-58]. Adherence to current guidelines on the appropriate dosage and monitoring of CsA can considerably decrease the risk of side effects [7, 59-62]. The mechanisms involved in many cyclosporine-induced side effects remain poorly understood, but they are thought to be partly due to calcineurin inhibition in nonlymphatic tissues [63]. The electrolyte disturbances are believed to be due to alterations in tubular function and thereby in ion homeostasis [29, 64]. The nephrotoxic effects have gained most attention over the years and have two components, an acute nephrotoxicity caused by vascular dysfunction and a more chronic fibrotic form.

Table 4. Common side effects of cyclosporine

Involved organs and systems	Adverse effect
Metabolism and nutrition disorders	Hyperlipidemia Anorexia Hyperuricemia Hyperkalemia Hypomagnesemia
Nervous system disorders	Tremor Headache Paresthesia
Cardiovascular disorders	Hypertension
Gastrointestinal disorders	Nausea Vomiting Abdominal pain Diarrhea Gingival hyperplasia
Hepatobiliary disorders	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Hypertrichosis
Muscoloskeletal disorders	Muscle cramps myalgia
Renal disorders	Renal dysfunction

Renal Dysfunction

Cyclosporine-induced renal dysfunction is the main concern when administrating CsA. However, most persistent renal dysfunction is related to prolonged therapy (ie, longer than 2 years) or doses greater than 5 mg/kd/day, both of which may result in structural renal changes [4, 45, 65-72].

The etiology of chronic CsA nephrotoxicity has been studied extensively. A combination of CsA-induced hemodynamic changes and direct toxic effects of CsA on tubular epithelial cells is thought to play a role [73]. Renal dysfunction can be functional or structural. Functional impairment, which may be an acute effect, can be subdivided into vascular dysfunction and tubular dysfunction [45, 66, 69, 74].

Vascular dysfunction is caused by vasoconstriction of the afferent glomerular arterioles, leading to increased vascular resistance. This results in decreased renal glomerular filtration rate (GFR) and renal blood flow with decreased clearance of creatinine. Tubular dysfunction is characterized by decreased magnesium reabsorption, decreased uric acid excretion, decreased potassium and hydrogen ion secretion, and distal tubular acidosis. Hypomagnesemia, decreased bicarbonate concentration, hyperuricemia, and hyperkalemia may also result [75].

Acute Nephrotoxicity

Murray et al in 1985 first suggested vasoconstriction of the afferent arterioles as one pathogenic mechanism for acute renal toxicity, possibly due to activation of the renal sympathetic nervous system, since a concomitant stimulation of plasma renin activity was demonstrated [76]. Barros et al also demonstrated an increase in vascular resistance in both afferent and efferent arterioles with a reduction in renal plasma flow and glomerular filtration rate (GFR), an effect that was attenuated by the administration of the angiotensin-converting enzyme (ACE) inhibitor captopril and the calcium channel blocker verapamil [77]. Activation of the RAS by CsA occurs by two mechanisms, a direct effect on juxtaglomerular cells [78] and indirectly through arterial vasoconstriction and reduced renal plasma flow.

In addition to its activation of the renin-angiotensin system (RAS), CsA has been shown to increase the vasoconstrictor factors endothelin and thromboxane, and to reduce vasodilator factors, such as prostacyclin, prostaglandin E2 and nitric oxide (NO) [79, 80]. Another pathogenic mechanism was that observed by Hoecherl et al, who demonstrated a marked reduction of COX-2 expression and of the downstream production of arachidonic acid metabolites, and a consequent vasoconstriction [79].

The role of the innate immune system has also been implicated in the nephrotoxicity of CsA. Injured tubular epithelial cells may activate toll-like receptors (TLR) and TNF-alfa, which, in turn, stimulate secretion of chemokines that initiate phagocytic activity and immune activation [82].

Chronic Nephrotoxicity

Chronic nephrotoxicity causes an obliterative microvascular renal injury (vasculopathy) and a tubulopathy.

Vasculopathy

Vasculopathy comprises glomerular or arteriolar thrombi, arteriolopathy, and interstitial fibrosis with tubular atrophy [83]. Thrombi are located in glomeruli or blood vessels. The arteriolopathy affects vessels in the peripheral vascular tree and is characterized by nodular protein deposits in the media consisting of immunoglobulin M and complement fractions (C3 and C1q), which replace necrotic myocytes in the arteriolar wall, narrowing or occluding the vascular lumen [84]. Mucoid thickening of the intimal wall can also occur. This leads to arteriolar hyalinosis, interstitial fibrosis [striped form], tubular atrophy, and glomerular sclerosis. In CsA-induced vasculopathy there may also be an increase in serum factor VIII and antithrombin III.

Tubulopathy

Tubular structural changes include isometric vacuolization of the proximal tubule, occasional giant mitochondria in tubular epithelial cells, single cell necrosis, and

microcalcification of TammeHorsfall protein in the distal tubule [74]. These changes are now rare, with the usage of lower CsA doses. While tubulopathic changes are reversible, vasculopathic changes are maintained in up to half of patients [74, 83].

Clinical Findings

From a clinical point of view, in cardiac transplant recipients surviving more than 12 months and treated with CsA at very high doses (up to 17 mg/kg/day), which are no longer used even in transplant medicine, Myers et al. observed significant reduction in GFR, renal plasma flow, and renal blood flow. Biopsies of five CsA-treated patients showed tubulointerstitial injury and focal glomerular sclerosis, which seemed to correlate in intensity with the degree of renal impairment (84). Further evidence of chronic nephrotoxicity related to high dose (>5mg/kg/die), long-term CsA use (> 2 years) was the finding of impaired renal function in heart, liver, and lung transplant recipients as well as in patients with autoimmune diseases [86-88]. More recently, other authors reported much more encouraging results following long-term use of CsA in kidney transplant recipients. In 638 cadaveric recipients treated with CsA for up to 15 years, patient and graft survival rates were 82.7% and 56.1% respectively and renal function remained stable in 46.6% patients, with preserved serum creatinine values [89]. Other authors studied the impact of continuing CsA-based immunosuppression in the second decade after kidney transplantation in 1,263 patients [90], observing that not all transplanted patients on long term CsA developed progressive renal changes, but conversely, in a subset or patients, serum creatinine levels were stable up to 20 years post-transplantation. These authors concluded that identifying recipients' predisposition to CsA toxicity and individualizing immunosuppressive therapy, possibly reducing CsA exposure over time, might improve long-term kidney function.

There have been many studies on the renal safety of long-term CsA therapy in autoimmune diseases. Feutren et al in 1992 studied the incidence of and the risk factors for CsA-induced nephropathy in 192 patients with various autoimmune diseases, including 63 children of ≤15 years of age [4]. The duration of CsA therapy ranged from 4 to 39 months and in most patients CsA doses were higher than currently recommended (8.2 ± 2.8 mg/kg/day). Renal biopsies were performed in all patients and 41 patients had evidence of CsA-induced nephropathy: Interstitial fibrosis with tubular atrophy were the predominant morphologic lesions in CsA-induced nephropathy. The percent increase in serum creatinine above baseline values was the best predictor of nephropathy. The dose of CsA, the type of underlying disease, and the patient's age were additional risk factors for nephropathy. The incidence of nephropathy was lower in children than in adults, probably because the clearance of CsA is greater in children [89]. This analysis suggests that in patients with autoimmune and inflammatory disease and normal renal function, the likelihood of the development of CsA-induced nephropathy can be minimized by using doses ≤ 5 mg/kg/day and avoiding increases in serum creatinine concentrations greater than 30% above the patient's baseline value by appropriate dose.

Several studies evaluated changes in renal structure, assessed in kidney biopsy specimens, together with the variation in GFR, in patients with psoriasis treated with CsA [46, 66, 68, 70, 72, 90-94]. Biopsy studies included a total of 104 patients receiving CsA for a

period ranging from 1 to 10 years at doses commonly ranging between 1.9 and 5 mg/kg/day, with some patients receiving up to 7.5 mg/kg/day. These studies showed slight to moderate interstitial fibrosis after 1 year of CsA in some subjects, and after 3 to 4 years, interstitial fibrosis was moderate to severe [66, 72, 92, 93]. The frequency of glomerular sclerosis in biopsies increased from 12.5% at 3 years to 26% at 10 years [70, 46]. Tubular atrophy, renal arteriolar abnormalities, consisting of either necrosis of smooth-muscle cells and nodular protein deposits in the wall of afferent glomerular arterioles, or arteriolar intima hyalinosis may also be seen [95]. Again, the percentage of increase in serum creatinine above 30% of baseline was found to be a predictor of structural kidney changes. Increases in serum creatinine were reversible 1 month to 10 years [46, 68, 96] after stopping CsA therapy. It seems that structural kidney damage can be expected in patients in whom serum creatinine does not decrease after cessation of CsA therapy. Young et al showed that older patients may be more vulnerable to CsA-induced renal injury [66]; other risk factors for cyclosporine-induced nephropathy include preexisting or new-onset hypertension, preexisting renal conditions, other nephrotoxic medications, and obesity [4, 69, 95]. Concerning rheumatoid arthritis (RA), the 1994 International Consensus Report on CsA treatment of RA concluded that CsA-induced nephropathy can be avoided when the following rules are observed: the starting dose should be 2.5-3.5 mg/kg/day, the maximum daily dose should not exceed 5 mg/kg/day and the dose should be reduced whenever serum creatinine increases by $\geq$ 30% [96, 97].

Hypertension

The reported incidence for hypertension during CsA treatment varies from 0 to 57% according to the different studies. Typically, hypertension showed a higher incidence in long-term treatment studies, while in short-course treatments showed to be less frequent (<24%) and completely reversible upon discontinuation [98, 99]. In a study of long-term therapy in 122 patients, the median time to development of hypertension was 55 months [99]. In this group, the onset of hypertension was bimodal, with a peak during the first 9 months of therapy and another after 36 months. Even longer-term studies have shown the persistence of hypertension after treatment in up to 35% of patients [100].

Different studies have shown a lack of relationship between the dose of CsA and the frequency of new-onset hypertension [73, 100, 101]. In a pooled analysis of 10 studies in psoriasis patients, hypertension occurred in 10.6% of those taking 2.5 mg/kg/day and in 11.9% of those taking 5 mg/kg/day. It has been hypothesized that a subset of patients may have increased individual sensitivity to CsA, developing hypertension even at low doses. That is why it has been proposed that CsA-induced hypertension may not always be reversible on dose reduction and should be managed by antihypertensive therapy [102]. There appears to be a lower incidence of new-onset hypertension in studies of short-term CsA treatment. In adults with atopic dermatitis, incidence of hypertension showed to be lower compared with studies of psoriasis, possibly reflecting a younger mean age of atopic dermatitis patients or a higher intrinsic risk of developing hypertension in psoriasis patients [103, 104]. In a large systematic review and meta-analysis of 15 studies of CsA in atopic dermatitis, seven studies showed no newly diagnosed hypertension [105]. In the pooled analysis of adult patients only, the incidence per month of newly diagnosed hypertension was a 1.6%.

During CsA treatment, blood pressure should be monitored regularly and appropriate management introduced as soon as there is evidence of CsA-induced hypertension. The current guidelines recommend a dose reduction of 25% to 50% if possible or the introduction of antihypertensive therapy [7, 60, 61]. Dihydropyridine calcium channels blockers, such as amlodipine or isradipine, are the antihypertensives of choice in CsA-associated hypertension, while verapamil and diltiazem should be avoided because they interfere with serum CsA levels, and nifedipine can potentiate the gingival hypertrophy caused by CsA. Potassium-sparing diuretics should also be avoided, because cyclosporine can increase serum potassium.

Neurologic Side Effects

Headaches, tremor, seizures, psychosis, paresthesias, and sleep disturbances have been associated with CsA treatment. Headache has been reported in up to half of patients, while paresthesias and tremor were observed in up to 40% and 26% of patients, respectively. Paresthesia and tremor often occur in the first weeks of treatment and improve over time without reduction of the dose: it has been hypothesized that hypomagnesemia may be the cause [106, 107]. Seizures have also rarely been reported, and those with a history of epilepsy should be warned that CsA can lower the seizure threshold. The risk of seizures is increased in those taking high doses of prednisone, prednisolone, or methlyprednisolone. Pseudotumor cerebri has been reported in some pediatric patients treated with CsA, particularly if administered concomitantly to tetracyclines [108-110]. The condition is rapidly reversible on withdrawal of CsA.

Gastrointestinal Side Effects

Gastrointestinal side effects include nausea, vomiting, diarrhea, or flatulence, which have been reported with relatively low incidence, ranging between 1% (vomiting and diarrhea) and 4% (nausea) [111]. Hyperbilirubinemia has been reported in up to 30% CsA treated patients, but in the absence of other alterations in liver function it does not require further assessments [61]. The cause may be the competitive inhibition of transport between bilirubin and CsA rather than direct hepatotoxicity [112]. Aminotransferases may also be increased in up to 30% of patients [61]. A reduction in CsA dosage may be required if bilirubin and transaminases exceed twice the normal values. Cholelithiasis has been reported with increased incidence in transplant recipients.

Gingival Hyperplasia

Gingival hyperplasia is rather frequent in long term CsA treated patients (up to 30%), especially in children, and is thought to be caused by fibrous hyperplasia. Genetic heterogeneity and poor oral hygiene seems to be implicated in its pathogenesis [113, 114]. The main consequences are esthetic, together with increase in caries and functional problems. Accurate oral hygiene ensuring plaque control and removal of local irritants may be of

benefit. Treatment with metronidazole induced complete resolution in a small published series [115].

Cutaneous Side Effects

Hypertrichosis is the most frequent among cutaneous side effects with a widely variable incidence ranging from 6% to 54% in different published series [96, 111, 116]. In a study in renal transplant recipients, hypertrichosis has been reported in 60%, epidermal cysts in 28%, keratosis pilaris in 21%, acne in 15%, folliculitis in 12%, and sebaceous hyperplasia in 10% of patients [117]. Pathogenesis has not been clarified yet, however it is known that CsA modulates protein kinase C expression and translocation in hair epithelial cells and promotes proliferation of these cells [118], and also prolongs human hair growth in vitro [119]. Other cutaneous side effects also affect the pilosebaceous unit, and studies have suggested that the follicular epithelium may be particularly sensitive to CsA [118]. Acneiform eruptions on pre-existing acne have been commonly reported [120]. In a large study conducted in 400 psoriasis patients undergoing an intermittent CsA regimen, transient palmar and/or plantar pustular psoriasis occurred in 5 patients on withdrawal of the drug, but did not require treatment discontinuation [98].

Risk of Malignancies

As for other immunosuppressive treatments, an increased risk of malignancies, particularly lymphomas and lymphoproliferative disorders, has been reported in transplant recipients following long-term treatment with CsA [121, 122]. However, it has to be considered that post-transplant patients receive high dose multiple immunosuppressive regimens. Long term post-transplantation studies have shown an increased risk of lymphoma. There have been isolated case reports of the development of B- and T-cell lymphomas in psoriasis patients treated with cyclosporine [123-126]. There was no increase, however, in the occurrence of lymphomas in the 1252 psoriasis patients described by Paul et al [127]. In the Sandoz Pharma study [111], three of the 842 psoriasis patients developed benign cutaneous lymphoproliferative disorders, another developed a B-cell lymphoma, and one a cutaneous T-cell lymphoma. The benign cutaneous lymphoproliferative disorders and B-cell lymphoma regressed rapidly on withdrawal of CsA. It is important to note, however, that psoriasis itself causes a state of chronic overactivation of the immune system, with a higher incidence of lymphoma and other malignancies than in non-psoriatic population [128, 129]. CsA has been shown to promote Epstein Barr virus [EBV] transformation of human peripheral blood lymphocytes [130]. One report described the development of EBV-associated lymphoproliferative disease after long-term CsA use, with spontaneous regression on withdrawal of the drug [131]. Other lymphoproliferative disorders, such as hairy cell leukemia and Waldenstrom macroglobulemia, have been reported [132].

Regarding solid tumors, there was no increased incidence in the psoriasis study by Paul et al [127], while in the Sandoz Pharma study five patients (0.7%) developed solid organ tumors, which however were considered unlikely to be CsA-related by the reporting physicians. Interestingly, in large case-control studies of patients treated with CsA in

combination with other immunosuppressive agents, a decreased odds ratio of rectal and breast cancers was observed [133, 134]. In general, the risk of malignancies increases with intensity and duration of therapy.

Infections

Despite its immunosuppressive effects, infections have been rarely reported on CsA treatment, generally recovering spontaneously or with appropriate antimicrobial treatment [106]. No increased risk of opportunistic infections or reactivation of tuberculosis was observed over 20 years of safety data in dermatologic patients [135]. However, since reactivation of latent tuberculosis has been reported in high dose treated transplant recipients, guidelines recommend to screen patients for latent tuberculosis before starting immunosuppression by CsA [136, 137].

Laboratory Abnormalities

Hyperlipidemia and particularly hypertriglyceridemia are frequent and well known adverse effects of CsA treatment. The product labeling reports hypertriglyceridemia in 15% of patients and hypercholesterolemia in <3% of patients. Clinical studies reported increases in triglycerides >30% above upper normal limits in 12 to 50% of patients and in cholesterol in up to 20% of patients [57, 138]. Increases in serum lipids generally occur in the first weeks of treatment, peak at 1 month and values return to normal at discontinuation of CsA [112, 139, 140]. Hyperlipidemia has been suggested to accelerate atherosclerosis in renal transplant patients [140]. Given that psoriasis patients have an increased risk to develop metabolic syndrome and cardiovascular morbidity, hyperlipidemia needs to be actively monitored and managed in psoriasis. In case of hyperlipidemia, a lipid-lowering diet is recommended and if this is not enough, CsA dose should be reduced and a lipid-lowering agent should be introduced. However, statins should be used with caution and careful clinical monitoring, since CsA decreases statin clearance and rhabdomyolysis may occur, though rarely, in case of concomitant therapy [141]. It has also been reported that concomitant fibrates administration may increase the risk of nephrotoxicity and renal failure [142].

Other laboratory abnormalities include hypomagnesemia, hyperuricemia, and hyperkalemia. Hyperkalemia is likely due to tubular dysfunction and secondary hypoaldosteronism [143].

Increases in alkaline phosphatase have been reported, in the absence of other liver function test abnormalities (106), and are probably related to changes in bone metabolism and subsequent increase in the bone alkaline phosphatase isoenzyme (30). In fact, CsA has been shown to cause mild osteoblastic proliferation and matrix mineralization activity in renal transplant patients with normal parathyroid hormone levels [144].

Conclusion

CsA is a potent immunosuppressive agent, which retains a crucial role in solid organ transplantations and has a well established effectiveness in autoimmune diseases. Its safety profile remains acceptable despite several reported side-effects. Attention should be paid to concomitant medications, due to many well known drug-drug interactions at both pharmacokinetic and pharmacodynamic level. Adverse effects are usually associated with longer treatment duration, larger cumulative doses and higher daily dose of CsA, and their prevalence with doses ≤5 mg/kg daily is low. In order to limit the risk of renal damage, which is the most feared adverse effect of long term CsA treatment, patients should be evaluated for factors that might increase their individual risk of nephrotoxicity. Patients' accurate baseline screening, careful monitoring and dose reduction are generally effective in controlling side effects, which are mostly completely reversible upon drug withdrawal. Intermittent therapy may offer a good therapeutic strategy to limit adverse effects, particularly nephrotoxicity, in long-term renal therapy, given the fact that most CsA side effects are dose- and time-dependent.

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