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CYCLOSPORINE IN RENAL TRANSPLANTATION: A REVIEW OF CLINICAL AND EXPERIMENTAL STUDIES

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After the first human kidney transplant in 1954 (Hume et al., 1955), a series of important discoveries gradually improved the sucess rate of kidney transplantation over the next 20 years.

The introduction of azathioprine (Imuran), in the early 1960s, for maintenance immunosuppression and the use of corticosteroids for the treatment of acute rejections aided engraftment. In the 1970s, the salubrious effect of blood transfusions on engraftment was first recognized (Opelz et al., 1973). Since that time, however, the management of transplant recipients has undergone little change.

The recent introduction of cyclosporine (CsA - Sandimmune), a potent immunossupressive agent (Calne et al., 1978), promises to be another milestone in transplantation.

The aim of the present article is to review the results of differents clinical trials and discuss the immunological mechanisms that account for prolonged allograft acceptance or tolerance induction observed after a treatment with CsA.

CLINICAL TRIALS

Calne and associates (Calne et al., 1978) where the first to use cyclosporine in recipients of mismatched cadaver kidney grafts. The one-year graft survival rate in patients treated with cyclosporine alone was 86% – a success rate clearly superior to that seen in historical controls.

Starzl and co-workers (Starzl et al., 1980) obtained similar results. However, both groups observed a substancial number of patients with impaired graft function. As a result, Starzl's group adopted a protocol combining cyclosporine with maintenance prednisone immunosuppression.

Since these early trials, a number of multicenter and singlecenter studies have compared cyclosporine to different standard immunosuppressive protocols in randomized controlled fashion. The results of these comparative studies are summarized in Table.

One-year patient survival rates in cyclosporine-treated patients exceeded 90% in all these trial. However, actuarial one-year graft survival rates in cyclosporine recipients varied widely (from 70% to 90%) among the centers. In contrast, graft survival rates in patients receiving standard treatment protocols ranged from 50% to 85%.

In all of these series, the rate of engraftment was higher in patients treated with cyclosporine than in those treated with azathioprine and prednisone.

The differences in graft survival rates between cyclosporine recipients and recipients of standard therapy reached statistical significance only in studies where graft survival rates were less than 70% in the control group. These results suggest that cyclosporine may benefit mainly those patient sub-groups in whom standard protocols have not yielded "optimal" survival rates.

Such high-risk groups include, for example, recipients of haplo-identical living-related-donor kidneys with high recipient antidonor mixed lymphocyte culture assays in vitro (Kahan et al., 1983). In fact, cyclosporine has increased one-year graft survival from 40% to 70% in patients who had previously lost a renal allograft due to rejection and in elderly patients (Rindgen et al., 1983).

In living related transplantation Kahan group (Fletchener et al., 1983) have shown an impressive survival of 100% and 95% for patient and graft respectively.

Thus it can be seen that cyclosporine has made a most impressive debut in renal transplantation in terms of patient and graft survival.

TABLE

Clinical trials comparing cyclosporine to standard immunossupressive protocols

Trial	Type of transplant	Protocols	No. of Patients	1-yr patient survival, %	1-yr graft survival, %		Graft function at 1 yr, serum creatinine (μmol/L)		Rejection, incidence/ total episodes	Infections, incidency/ total episodes	
										All Infections	Viral Infections
AUSTRALIAN	CAD	CsA	30	93	70	NS	180*		83%	31	7
multicenter		A+P+ATG	30	97	80		119*		93%	47	17
(Sheil et al., 1983)											
CANADIAN	CAD	CsA+P	103	97	80	P=0,003	195	P=0,03	159+	81+	18+
multicenter		A+P+ATG+	107	89	64		149		157	99	27
(N. Engl. J.Med. 1983)											
EUROPEAN	CAD	CsA	117	94	72	P=0,001	184	P=0,001	86%	–	–
multicenter		A+P	115	92	52		169		91%	–	-
(Lancet, 1983)											
BIRMINGHAM	CAD	CsA+P§	35	94	77	NS	227	P=0,02	63%	48%	17%
(MacMaste et al, 1983)		A+P	33	91	85		121		64%	72%	15%
BOSTON	CAD	CsA+P	76	95	78	P=0,01	–		53%	30%	10%
(Tilney et al., 1984)		A+P	36	93	53		–		72%	18%	7%
DENVER	CAD	CsA+P	38	99	90	P=0,02	174	NS	–	-	
PITTSBURGH		A+P	32	99	50		142		-	–	–
(Rosenthal et al., 1983)											
MINNEAPOLIS	CAD or	CsA+P	92	92	87	NS	194	P=0,05	31%	47%	24%
(Najarian et al., 1983)	LRD	A+P+ATG	90	95	80		133		58%	60%	63

Key: CAD = cadaver kidney; LRD = living-related-donor kidney; CsA = cyclosporine (Sandimmune); A = azathioprine (Imuran); P = prednisone; ATG = lymphocyte immune globulin (antithymocyte globulin [Atgam]); NS = not significant
* Lowest level
+ Only some of the control patients received ATG
‡ Total episodes
§ Given for 14 days only.

MECHANISM OF ACTION

The remarkable efficacy of CsA to prolong allogeneic graft survival in laboratory animals and man has prompted many studies to investigate the mechanism by which it induces transplantation tolerance.

Initial studies have demonstrated that the predominant effect of CsA action in vitro is directed against T helper (Th) lymphocytes by hampering their production and/or release of interleukin 2 (IL-2) (Borel et al., 1976; Hess et al., 1982; Bunjes et al., 1981) and preventing their activation by reducing the availability of interleukin 1 (IL-1) (Bunjes et al., 1981). While inhibiting the generation of T cytotoxic lymphocytes (Tc) in response to transplantation antigens, CsA has also shown to have a soaring effect on the establishment of suppressor cell (Ts) regulatory system, creating desequilibrium in the immune network between Ts and Tc (Kupiec-Weglinski et al., 1984).

The release of other lymphokines, such as gamma-interferon, by activated T cell is also inhibited by CsA (Kalman & Klimpel 1983; Thomson et al., 1983). We have recently shown that in vivo CsA therapy inhibits monocyte (IL-1 release) as well as lymphocyte function (IL-2 and IL-3 release) only during active CsA treatment (Abbud-Filho et al., 1985). Once the drug is withdrawn interleukins release returns to normal at 3-4 weeks after transplantation. These and others observations support the concept that the state of unresponsiviness is governed by suppressor cells (Kupiec-Weglinski et al., 1984; Abbud-filho et al., 1984; Kupiec-Weglinski et al., 1985) and long-term graft acceptance is not due solely to dampened helper cell capabilities.

The concept of the emergence of, at least two populations of Ts as mediators of host mechanisms and immunoregulation of alloresponsiveness is becoming increasingly accepted (Kupiec-Weglinski et al., 1984). Tutschaka et al. (1979) observed an accelerated appearance of Ts following bone marrow transplantation that may have contributed to the absence of GVHD in CsA treated rats. Hutchinson et al. (1981) and Kupiec-Weglinski et al. (1983) demonstrated that adoptive transfer of splenocytes or thymocytes from CsA-treated rats heart graft recipients caused significant prolongation of test cardiac allograft placed in otherwise untreated, syngeneic, immunologicalilly virgin rats. This effect was antigen-specific, as ascertained in vivo using specific and third-party graft donors, and in vitro in a mixed lymphocyte reaction. Transfer of cells from normal rats, CsA-treated but ungrafted animals, or grafted but untreated recipients, all failed to prolong test graft survival.

A recent report (Bordez-Aznar et al., 1983) subdivide into three stages the kinetics and specificity of CsA-mediated transplantation tolerance: stage 1, coincides with cessation of CsA therapy at day 7, at wich time a nonspecific and unstable state of tolerance is present – the survival of a second graft being moderately prolonged regardless of its antigen specificity; stage 2, when second grafts were placed 14 days following the initial transplantation, the second specific grafts survived at least 2 month, whereas all third party grafts were rejected within 10 days; stage 3, 50 or more days following the initial transplantation, stable specific unresponsiveness was manifested in CsA-treated recipients, because both first and second specific grafts survive indefinitely, but third-party grafts were rejected acutely without affecting the original transplant. Thus, the explanation that a specific and stable state of CsA-induced unresponsiveness in vivo develops in time, and may be due to gradual proliferation of specific Ts, is highly probable.

In a serie of experiments Kupiec-Weglinski et al. trying to recreate the events of acute rejection of long-term cardiac allograft in CsA-modified recipients, found that transfer of large amounts of specifically sensitized lymphocytes (sSL) were ineffectual in restoring host in immunocompetence, even when the inocula was supplemented with IL-2 CM. However, if the animals were challenged with cyclophosphamide (Cy), an agent reputed to destroy Ts (Rollingoff et al., 1977), followed by infusion of sSL ± IL-2 CM, acute rejection was reproduced at a tempo similar to that in untreated control recipients. Reestablishment of immune responsiveness could be inhibited by subsequent transfer of splenic lymphocytes from CsA, but not CsA + Cy modified and grafted hosts (Kupiec-Weglinski et al., 1982; 1983a, b). These results provided direct evidence that CsA recipients contain Cy-sensitive T cells that suppress the action of passively transfered sSL. Hence, CsA might allow the development of an active mechanism of suppression, mediated by Cy-sensitive Ts in vivo, which produce soluble mediators ultimately responsible for allograft survival and abrogate profundly host effector responses against organ allografts.

Further adoptive transfer studies using rat recipients of cardiac allografts treated with CsA and T cell-deprived hosts (B rats) have recently shown that an responsive state in CsA-treated animals is achieved despite the presence of fully potent donor-specific Th. However when CsA-Th lymphocytes are recombined with CsA-Tc/s in their normal ratio and transfered into B rats they lost the ability to promote allograft rejection (Kupiec-Weglinski et al., 1985). Such a finding emphasizes exceptional efficacy of Ts in sustaining CsA-mediated allograft survival and stresses the ability of these cells to supress the targets of the rejection cascade. In these studies we also demonstrate that small amount of CsA-Ts/c lymphocytes was responsible for the inability of a large number of CsA-Th to augment the immune response and induce acute graft rejections therefore stressing the potency of that CsA-induced suppressor cell population. Interestingly, we have demonstrated that during the "tolerant" phase of cardiac allografts release of interleukins (IL-1 and IL-2) mitogen-induced was quantitatively similar to that noted in normal animals. In contrast, a remarkable increase in the production of IL-3 was observed in the tolerant group. The correlation of increased spontaneous productions of IL-3 and the emergence of suppressor cells lead us to postule that this interleukin may be implicated in the activation of clonal expansion of suppressor cells (Abbud-Filho et al., 1984). Recently using a monoclonal antibody binding specifically to the IL-2R molecule (ART 18) to prevent/treat acute rejection, the Boston group also found an increased IL-3 production in ART 18 treated recipients while diminishing IL-2 release (Kupiec-Weglinski et al., 1986).

Despite important recent progress the subcellular sites of CsA action are unknown. It is deduced from a large number of both in vitro and in vivo experiments, that CsA may interact at three different sites of the lymphocytes: at level of membrane, within the cytoplasm and/or at the nuclear level.

Interaction at the level of lymphocyte membrane – The effects of CsA on the IL-2R has been controversial. Initial functional studies have suggested that CsA inhibits the precursor of Tc (p CTL) from acquire receptors to the IL-2 (Larson, 1980; Hess et al., 1982). Further results in the human MLR system provided evidence on the ability of CsA to prevent the development of functional IL-2 responsiveness of the CTL by CsA and raised the hypothesis that adequate levels of the drug must be achieved early in vivo to prevent sensitization of the pCTL (Hess, 1985).

However, by using monoclonal antibody capable of detect the IL-2R (Tac) Miyawaki et

al. demonstrated that CsA did not inhibit Tac expression on mitogen stimulated human lymphocytes (Miyawaki et al., 1983). Comparable results on Tac expression were obtained by Ryfel et al. (1985) while Lillehoj et al. (1984) in the mouse, demonstrated contrary results.

Several others activation antigens expressed on T lymphocytes were also tested. Class II histocompatibility antigens (HLA-DR), transferrin receptors and those antigens detected by OKT 9 and OKT 10 monoclonal antibodies were reduced in the presence of CsA (Miyawaki et al., 1983; Leapman et al., 1982). Prolactin receptors are also affected as CsA and prolactin compete actively for similar binding sites.

Aditional effect of CsA at level of membrane is its action on the MHC products. CsA has recently been shwon to prevent induction of class II antigen expression by immunologic stimuli, probably by direct inhibition of gamma interferon production or via suppression of IL-2 release (Halloran et al., 1985; Groenewegen et al., 1985). Until now no specific receptor protein binding to CsA has been demonstrated.

Interaction of CsA within the cytoplasm – Merker & Handshumacher (1984) performing uptake studies with radiolabelled CsA found 70-80% of the drug was concentrated in the cytosol of lysed cells. They have further shown that uptake of CsA is largely due to a 17-kilodalton basic protein found predominantly in the cytoplasmic fractions from a number of cell types. That protein was termed "cyclophilin" (Merker & Handshumacher, 1984).

Another protein, calmodulin, a cytosolic calcium-dependent regulator protein is also affected by CsA. Recent studies demonstrated that CsA binds to calmodulin and inhibits calmodulin-dependent enzymatic activation (Colombani et al., 1985) Calmodulin inhibition by CsA may imply in: 1) prevention of glycogen breakdown and phosphorylation of kinases with consequent ATP depletion (Lum et al., 1984); 2) increased prostaglandin E_2 production by the macrophage (Whisler et al., 1984); 3) activation of protein kinase C (Block et al., 1980); 4) prevention of DNA and mRNA synthesis (Hirano et al., 1984). All these leading to inhibition of Th and Tc lymphocytes division-proliferation and activation of Ts lymphocytes.

CsA did not appear to interfere with mitogen or alloantigen binding to T lymphocytes neither with calcium influx secondary to membrane binding (Metclalf, 1984).

Interaction of CsA at the nuclear level – Studies with labelled CsA have demonstrated nuclear localization of the drug (Merker & Handschumacher, 1984). This finding is important since recent reports have shown that specific mRNA synthesis for lymphokines is inhibited by CsA (Elliot et al., 1984; Kronke et al., 1984). This action might be the most important step to inhibit the rejection cascade as it is known that mRNA transcription of lymphokines occurs within a few hours after stimulation of resting lymphocytes and reaches maximal concentration during the transition from the G_0 / G_1 to the S phase of T cell cycle. While expression of IL-2R, HT_3 and actin genes are not inhibited by CsA, suppression of IL-2, gamma-interferon, B cell and cytolitic factors does occurs (Kromke et al., 1984; Wiskocil et al., 1985).

GENERAL COMMENTS

It is inquestionable the efficacy of CsA as immunosuppressive agent. Over the past ten year multiple clinical trials have confirmed that graft survival rates are higher in patients treated with CsA than in those given conventional immunosuppression. The optimal dosage of the drug has not yet been established and nephrotoxicity is the most important complication of its use.

The precise mechanism of action CsA remains unclear despite important recent progress. It appears that CsA interferes with particular stages in the immune responses participing in allograft destruction by interfering with proliferation of various stimulated lymphoide cells, by suppression of release of monokine (IL-1) and lymphokines (IL-2, IL-3, gamma-interferon). Additionally CsA affects proliferation and maturation of CTL. In contrast, the activation of suppressor T lymphocytes and the mechanism of amplification for Ts are not affected by the drug.

Interestingly, an unresponsive state can be achieved in CsA-treated animals despite the presence of fully potent donor-specific Th. We have provided some evidence that IL-3 might be a trophic factor for the clonal expansion of Ts and hence may play a role in graft tolerance.

CsA may also modulate the immune response by blocking polyamine synthesis and as an antagonist of the prolactine receptor. Inhibition of MHC products induction may also contribute to the immunosuppressive action of CsA.

At the molecular level recent studies have shown the CsA interferes with some cell activation antigens althouth its effects on the IL-2R expression remains contraversial. Inhibition of the DNA-RNA transcriptional process required for IL-2 production does occurs as well as a blockade of calmodulin with subsequent impairment of enzymatic pathways necessary to mRNA protein synthesis and cell division/proliferation.

The purpose of this review was to unify findings of literature and ourselves and to demonstrate that CsA interacts in a complex way with differents pathways of the immune system.

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