

Ciclosporin (Cyclosporin A): Prototype of a New Generation of Immunosuppressive Drugs

K. BENDTZEN

Medical Department TA, The State University Hospital, Copenhagen, Denmark

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At Sandoz Ltd., Switzerland, samples of soil are routinely screened for biologically active metabolites produced by microorganisms. In the late 'sixties, such a sample, collected from the Hardanger Vidda in Norway, was found to contain a strain of fungi (*Tolypocladium inflatum* Gams) which in their mycelium harboured a water-insoluble substance with a restricted range of fungistatic activity (12). In 1972, Borel discovered that this metabolite, originally named cyclosporin A, was a potent inhibitor of the antibody response in rodents despite a complete lack of cytostatic property (12). Later, the unique T-lymphocyte-suppressive function of cyclosporin A was revealed (13). In 1977/78, the first clinical trials were conducted, following animal studies that confirmed its ability to prolong organ allograft survival and to prevent graft-versus-host disease in recipients of allogeneic bone-marrow (17,40). In 1973, cyclosporin A was purified, and in 1975, its unique structure was elucidated (see ref. 52). The molecule, whose "International Nonproprietary Name (INN)" is ciclosporin (Cs), is only one of several related peptides, some of which also suppress the immune function. It is a highly hydrophobic, cyclic peptide consisting of 11 aminoacids most of which are N-methylated. One of these is unique to this molecular species and

is essential for their immunosuppressive properties (Fig. 1). Cs can now be synthesized, but the synthesis is still troublesome and there is no practical alternative to the microbiological manufacture of the drug by fermentation of the fungus and subsequent extraction.

IMMUNOSUPPRESSIVE PROPERTY

B-lymphocyte-mediated immunity

Cs inhibits primary and, less efficaciously, secondary antibody responses to T-cell-dependent antigens. The action is reversible, dose-dependent and most effective if the drug is administered before the antigenic stimulus (14). Cs does not suppress B-lymphocyte responses to T-cell-independent antigens in the congenitally athymic, T-cell-deficient "nude mouse" (14), and also fails to affect the antibody response to T-cell-independent B-lymphocyte-activators in other rodents (14), as well as in man (51). One is therefore inclined to believe that Cs selectively impairs the function and even the number of T-helper-cells, an assumption supported by its direct effect on T-lymphocyte responses (see below) and, more indirectly, by its ability

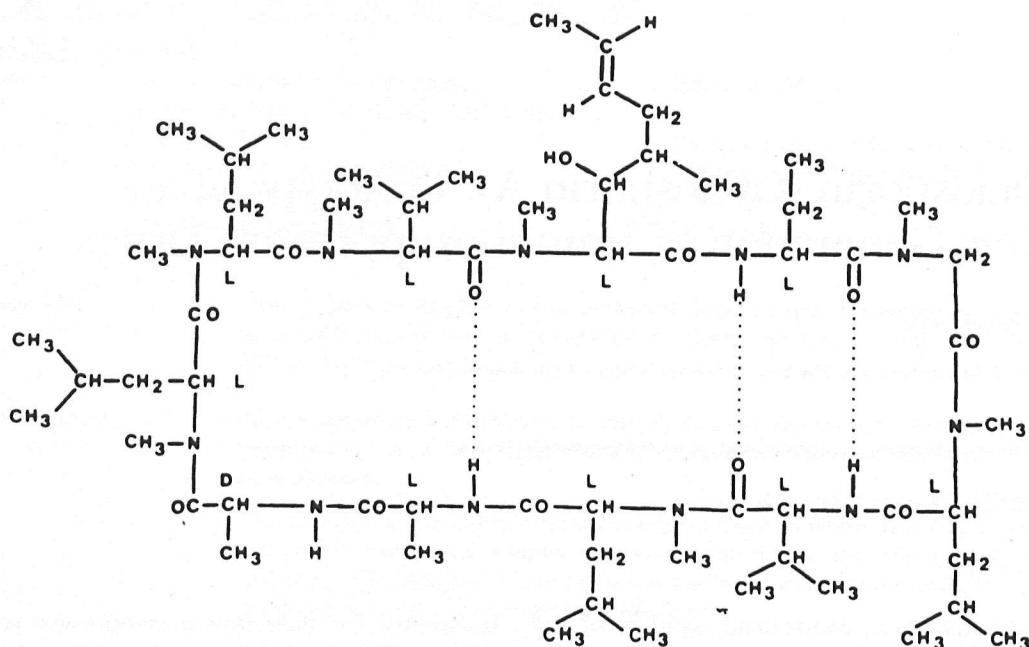


Fig. 1. Structure of ciclosporin. The unsaturated hydrocarbon chain shown at the top belongs to a hitherto unknown amino acid. The molecule is extensively N-methylated and therefore very hydrophobic.

to deplete medullary thymocytes and splenic T-cells (2).

T-lymphocyte-mediated immunity

Cs is a very potent inhibitor of delayed-type hypersensitivity responses *in vivo* as well as other T-lymphocyte responses evoked *in vitro* by recall antigens, alloantigens, and some T-cell polyclonal activators (6–8, 22–24). Cs appears to block reversibly the initial macrophage – T-lymphocyte cooperative processes (4). This impairs the production by the T-helper-cell of interleukin 2, the function of which is mandatory for T-lymphocyte proliferation and differentiation to cytotoxic T-cells (4,16,23,30). Mature cytotoxic T-cells, and cells already proliferating, are not affected by Cs; this is to be expected on the basis of kinetic studies showing effects of the drug on the G_0 – G_1 phase of the T-cell cycle (6–8,22). Since T-lymphocyte mediators are also required for B-cell growth and differentiation, this blocking of lymphokine production also ex-

plains the suppressive function of Cs on T-cell-dependent antibody production (35).

An effect of Cs on T-suppressor-cells is not likely, but cannot be excluded (25). In therapeutic concentrations, the peptide does not suppress the *in vitro* function of human NK-cells whether or not they are stimulated by interferon (Pedersen & Bendtzen, unpublished findings). However, mice treated with rather high doses of Cs fail to develop a normal NK response, and they also do not mount a normal antibody-dependent cell-mediated cytotoxic response (1). Whether or not the latter was mediated by lymphocytes (K-cells) or macrophages, these results suggest that Cs interferes with central controlling mechanisms involved in the development and/or maintenance of the cell types responsible for these cytotoxic activities.

Nonspecific inflammation

Can Cs alter the function of cells other than lymphocytes? The peptide does not directly

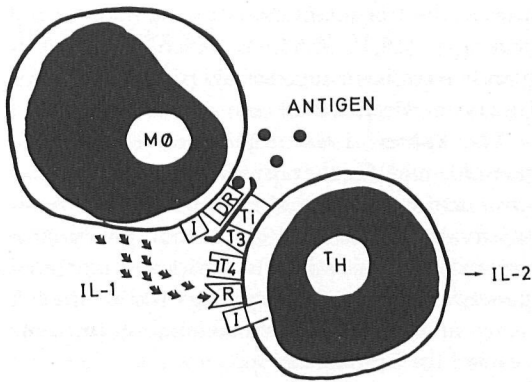


Fig. 2. Proposed model of T-lymphocyte receptors that might be involved in the molecular mechanism of action of ciclosporin (Cs).

Ti is a 43K clonotypic structure which, in association with 20K T3, defines the specific T-cell receptor. The T3-Ti complex appears to recognize soluble antigen (●) in the context of MHC antigens. T4 is the 62K associative recognition element for class II molecules (44).

Insulin receptors are present on resting macrophages (MØ), presumably associated with MHC molecules. On unstimulated T-helper-lymphocytes (T_H) their numbers are sparse, but they are greatly increased after antigen- or polyclonal activation (21).

Cs may interfere reversibly with the depicted T-cell receptor complex, because:

- 1) it interferes with the binding of monoclonal antibodies to T4 (Bendtzen & Wiik, unpublished findings) and, possibly, to T3 (15);
- 2) it may block receptors for class II MHC molecules on T-cells (38);
- 3) exogenous interleukin 1 (IL-1) rectifies the pre-S-phase lymphokine response of Cs-treated T-cells (6-8), and Cs seems to interfere directly with the binding of IL-1 to T-lymphocytes (5); and
- 4) human and porcine insulin selectively rectify the pre-S-phase response of Cs-treated T-cells, the kinetics of which indicating interference with the antigen-recognition phase of the T-cell triggering process (5,9).

impair macrophage or granulocyte functions, except perhaps that Cs at high and *in vivo* unattainable concentrations inhibits the *in vitro* release of lactoferrin from neutrophils (28). Cs, however, does not interfere with the function of haemopoietic organs; of prime clinical importance. On the other hand, receptor studies show that although lymphocytes possess high affinity binding sites for Cs, the peptide also binds efficaciously to other cell types, including neutrophils and macro-

phages (Svenson & Bendtzen, unpublished results, and 32,43). Furthermore, recent investigations show that therapeutic concentrations of Cs directly inhibit histamine release from human basophils and rat mast cells stimulated by antigens, anti-IgE, lectins and calcium ionophore (39). Finally, Cs seems to interfere directly with the growth of certain protozoa, such as *Plasmodium falciparum* (36). The clinical importance of this finding is at present unknown.

MOLECULAR MECHANISM OF ACTION OF CICLOSPORIN

The exact locus of action of Cs on the T-lymphocyte is still enigmatic. The peptide has been said to interfere with the binding of OKT 3 monoclonal antibody, suggesting a binding of Cs close to the antigen and mitogen receptors on T-lymphocytes (15,38). Although we have not been able to confirm these findings, we have found that human and porcine insulin, but not insulins from lower animals, rectify the pre-S-phase lymphokine response of human T-cells challenged by recall antigen (5,9). Furthermore, indirect evidence indicates that Cs reversibly interferes with the function of the MØ-derived T-cell activator, interleukin 1, probably at a common receptor site on the T-lymphocyte (5-8). In this regard, it is interesting that preliminary findings in our laboratories indicate that interleukin 1 reduces T-cell-binding of OKT 4 (but not OKT 3 or OKT 8) monoclonal antibodies (Bendtzen & Wiik; unpublished). Since T3 and T4 molecules appear to be part of the structures involved in T-cell recognition (44), and since T-cell insulin receptors may be associated with these structures as well (33, and Fehlmann, personal communication), it is tempting to speculate that Cs binds (reversibly?) to molecule(s) within this complex, and also that interleukin 1 functions through a binding to this receptor complex. A schematic presentation of such a receptor complex is depicted in Fig. 2.

CLINICAL USE OF CICLOSPORIN

Allotransplantation

After the initial studies on the ability of Cs to suppress the rejection of heterotopic heart transplants in rats, numerous animal studies have confirmed the ability of Cs to prolong allograft and even xenograft survival (29, 50, 53, 54,). In Cs-treated animals, the following organs have been transplanted successfully: heart, lung, kidney, pancreas, liver, skin, muscle, nerve and Schwann cells, bone-marrow, small intestine, cornea, joint, leg, islets of Langerhans, ovaries and fallopian tubes. In many cases Cs appears to induce donor-specific tolerance, the ultimate goal in transplantation immunology, but the mechanism by which this is achieved is still unknown.

In humans, Cs was first used in 1977/78 for the prevention of renal allograft rejection (17) and graft-versus-host disease in allogeneic marrow transplantation (40). Since then Cs has become the drug of choice for maintenance of kidney, liver, heart and even combined heart-lung allografts, and the drug has important

uses in the transplantation of bone-marrow and pancreas (18,19,50,53,54). Even parathyroid glands have been successfully transplanted (Albrechtsen, D., personal communication).

The kidney is the organ most often transplanted, and Cs therapy has increased 1 year graft survivals from 55% (conventional therapy) to about 75% (18,19). These improvements are reflected also in a significantly increased patient survival (approaching 100% after 1 year) and a marked shortening of the time needed for hospitalization.

Transplantation of the liver was until recently plagued by very low survival rates (about 30% after 1 year). Cs therapy, however, has now improved these rates to more than 70% (45).

The advent of Cs treatment has also greatly improved the results of heart transplantations. The initial discouraging results were mostly caused by graft rejection. However, Cs therapy has now increased the 1 year survival rates to more than 60%, and in the case of cardiopulmonary transplantation, survivals of more than 1 year have been obtained (27).

In contrast to the experience in animal models, the induction of donor-specific unresponsiveness in humans has never been convincingly demonstrated. However, marrow grafts have been maintained in some patients after cessation of Cs therapy. Although the pre-transplantation conditioning of most of these patients (total body x-irradiation of high-dose cyclophosphamide) may have contributed to the development of tolerance, there is some evidence that pharmacological inhibition of interleukin 1 function may generate unresponsiveness (3). Thus, stimulation of human blood T-lymphocytes with a recall antigen in the presence of cadmium ions, phenanthroline, or penicillamine, which are all reversible inhibitors of interleukin 1, renders these T-cells unresponsive to a secondary challenge by the same antigen. Interestingly, however, this state of unresponsiveness is antigen-specific, since the cells respond normally to a different recall antigen. There is also circumstantial evidence that specific unresponsiveness may be mediated by a nylon wool adherent suppressor cell (24).

Table 1

Some autoimmune diseases that may benefit from treatment with ciclosporin

Rheumatoid arthritis with or without amyloidosis (local application?)* (20)
Psoriatic arthritis (skin lesions respond very well; local application?) (20)
Autoimmune uveitis* (37)
Behcet's disease* (37)
Polymyositis (10,55)
Idiopathic myocarditis*
Systemic lupus erythematosus (26)
Pulmonary sarcoidosis (42)
Aplastic anemia (48)
Primary biliary cirrhosis (49)
Malignant T cell lymphomas (41)
Wegener's granulomatosis?*
Graves ophthalmopathy?
Myasthenia gravis?
Multiple sclerosis?
Relapsing polyorchondritis?

* Bendtzen, K. et al.: unpublished findings.

Autoimmune diseases

Unlike the transplant situation, in which immunosuppression may be given prophylactically, the management of the more ill-defined autoimmune disorders fosters special problems, since these patients are already 'immunologically activated'. However, the therapeutic effects seen in several animal models, particularly in those genetically susceptible to the development of autoaggression, have now paved the way for a number of promising clinical studies. For instance, rodent adjuvant arthritis, experimental uveitis, encephalomyelitis, neuritis, nephritis, thyroiditis, myasthenia gravis and systemic lupus have all been successfully treated with Cs (50,53,54). Epithelioid granuloma formation and the development of caseating necrosis are also prevented in rats challenged by subcutaneous injections of mycobacteria (34). Since generalization of infection in these animals was absent, Cs may prove beneficial in the management of granulomatous diseases in humans as well. Interestingly, the spontaneously developing autoimmune diabetes in BB Wistar rats (resembling type I diabetes in humans) is also prevented by Cs prophylaxis (31).

Owing to the inherent problems of clinical trials in human autoimmune diseases, in which the pathogenetic mechanisms are often uncertain and multifactorial, the results of pilot studies are the only ones presently available. However, there are prospects that immune diseases, such as those shown in Table 1, may respond favourably to Cs therapy. One may even hope that with the assistance of Cs, it will be possible to define more precisely the defects underlying these disorders. Of great interest is the recent finding that type I diabetes may be prevented if treated immediately after diagnosis (47). Multicenter clinical studies on the effect of Cs in the management of multiple sclerosis, primary biliary cirrhosis and myasthenia gravis as well as type I diabetes are now under way.

Side effects

Cs has been used in humans since 1977, mostly for the prevention of allograft (kidney) rejection. By now, more than 3000 renal transplant

patients have received Cs therapy. The side effects encountered include nephrotoxicity, hepatotoxicity, upper gastrointestinal discomfort, burning sensations in hands and feet, tremor, hypertension, hirsutism and gum hypertrophy. All are frequent but dose-dependent and reversible. The risk of lymphoma development is increased, but apparently less so than if conventional immunosuppressive therapy is administered (18,19,33,50,54). Many of these lymphomas develop as a result of suppression of the cytotoxic T-cell response to B-lymphocytes transformed by Epstein-Barr-virus (11). Recent results indicate that these lymphomas may disappear simply by discontinuing the drug (46). The slightly increased occurrence of other viral or bacterial infections does not pose serious problems.

It should be noted that the bioavailability of Cs varies considerably, even in the same patient. It is therefore mandatory to monitor the blood or serum levels of the drug during the entire course of the treatment. This is especially true if Cs is given together with other pharmaceuticals. For example, erythromycin and ketoconazole abruptly increase Cs levels, whereas barbiturates and hydantoin derivatives diminish the concentrations of the drug.

CONCLUSION

Cs is the first of a new class of immunosuppressants with a hitherto unknown selectivity in its T-cell suppressive function. Its precise locus of action is still unknown, but the lipophilic molecule may alter the function of membrane structures intimately related with the T-cell receptors for antigen, class II MHC molecules, and interleukin 1; it may also interfere with the function of insulin receptors on antigen-presenting cells. It has no cytotoxic or acute antiinflammatory action, but inhibits T-cell-mediated reactions including chronic inflammation, development of cytotoxic T-lymphocytes, and antibody production in response to T-cell-dependent antigens or lectines. Though very expensive, Cs is the drug of choice in the prevention of clinical organ transplant rejection, and increased usage in the treatment of autoimmune disorders is expected.

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Address:

Klaus Bendtzen

Medical Department TA

University Hospital of Copenhagen

Tagensvej 20

DK-2200 Copenhagen N

Denmark

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