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Review Article

Cyclosporine (Ciclosporin): A Powerful Immunosuppressant

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ABSTRACT

Cyclosporine is an immunosuppressive drug that acts selectively on T-cells by inhibiting calcineurin phosphorylase. It has been used in dermatology since its approval by the US Food and Drug Administration in 1997 for use in psoriasis. While indicated only for the treatment of moderate to severe psoriasis, cyclosporine has also been used as an off-label drug for the treatment of various inflammatory skin conditions, including atopic dermatitis, blistering disorders, and connective tissue diseases. In this article, we review the use of cyclosporine in dermatology. Cyclosporin A (CyA) is a powerful immunosuppressive agent whose lack of myelotoxicity makes it unique among nonsteroidal drugs currently given for immunosuppression. It has been used with initial success in recipients of kidney, liver, bone marrow and pancreas transplants, and it may also have clinical application in the treatment of autoimmune disorders. Regarding its use in transplant recipients, there are many remaining questions about its mechanism of action, the optimum dose, whether it should be used alone or with other immunosuppressants, whether it can suppress chronic rejection and what its long-term side effects may be. These questions can only be answered by further careful laboratory investigation and controlled clinical trials. Until then, CyA should only be administered in centres experienced in its use.

INTRODUCTION

Cyclosporine is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It forms a complex with cyclophilin, a cytoplasmic immunophilin. This complex inactivates calcineurin phosphorylase, preventing the phosphorylation of nuclear factor of activated T-cells (NFAT) and, therefore, the production of NFAT-dependent cytokine such asin-interleukin-2, which is required for full activation of the T-cell path-way. Cyclosporine was the first immunosuppressive drug found to act selectively on T-cells. It was isolated in 1970 from the soil fungus Tolypocladium inflatum Gams by Borel at Sandoz Laboratories in D Basel, Switzerland while looking for novel antifungal agents.'

In 1979, cyclosporine was first observed to improve psoriasis during a pilot study undertaken

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to investigate the efficacy of cyclosporine in rheumatoid arthritis and psoriatic arthritis but was not approved by the US Food and Drug Administration for the treatment of psoriasis until 1997. Since then, the FDA has not approved cyclosporine for the treatment of any other clinical condition in dermatology; however, it has been approved for use in atopic dermatitis in other countries (Europe) and it has been used off-label for the treatment of multiple inflammatory skin conditions including blistering disorders, and connective tissue diseases. Cyclosporine is an immunosuppressive agent used to treat organ rejection post-transplant. It also has use in certain other autoimmune diseases, treatment of organ rejection in kidney, liver, and heart allogeneic transplants, and rheumatoid arthritis when the condition has not adequately responded to methotrexate. Also, it is a second-line agent for ALS and graft vs. host disease. It also has other FDA and non-FDA-approved indications. This activity reviews the mechanism of action, structure, adverse effects, administration, clinical uses, and side effects of cyclosporine, pertinent for interprofessional team members in treating conditions where cyclosporine is indicated.

Mechanism of Action:

yclosporine works to suppress cell-mediated immune reactions. Research has detected no effects on phagocytic function in animals, and it does not cause bone marrow suppression in animal or human models. The mechanism of action of cyclosporine is as a calcineurin inhibitor, a cytochrome P450 3A4 inhibitor, and a P-glycoprotein inhibitor. Cyclosporin A (CsA) inhibits the synthesis of interleukins (IL), including IL-2, which is essential for the self-activation of T lymphocytes (LT) and their differentiation. Cyclosporine is effective due to specific and reversible inhibition of immunocompetent lymphocytes in the G0 and G1-phase of the cell cycle. The T-helper cell is the primary target, although it may also suppress T-suppressor cells. The LT-B-lymphocyte (LB) cooperation is essential for the activation of LB; the latter also gets inhibited. In addition, research has demonstrated that CsA had an inhibiting effect on CD4+ CD25+ Tregs, which might block the host immune tolerance potentiality.

Metabolism: Via hepatic CYP3A4 and is metabolized into a pair of hydroxylated derivatives (AM1 and AM9) and one N-methylated derivative (AM4N).

Enzymes inhibited: CYP3A4 and P-glycoprotein.

Half-Life: 8.4 to 27 hours: The time to peak blood cyclosporine concentrations (Tmax) ranges from 1.5 to 2 hours following oral administration of cyclosporine oral solution USP modified.

Clearance: 5 to 7 mL/min/kg in patients who are recipients of renal or liver allografts while appearing to be somewhat slower in cardiac transplant patients.

Excretion: Mainly bile and feces.

Factors known to influence absorption: Time post-transplant, bile flow, dietary composition, gastrointestinal state, liver function, small bowel length, and vehicle.

Structure:

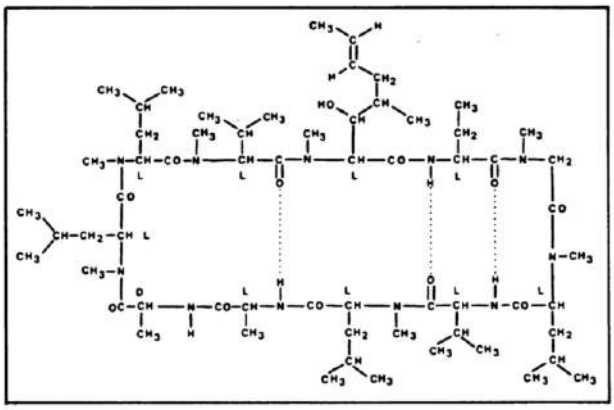

FIG. 1—Molecular structure of cyclosporin A (CyA).

Adverse Effects:

Cardiovascular: Hypertension, arrhythmia.

Renal: Decreases glomerular filtration rate (GFR) due to an increased tone of the glomerular afferent arterioles. Serum creatinine concentration rises

and decreases creatinine clearance. The undesirable effects correlate with the duration of treatment and dose.

Endocrinological and metabolic: Dyslipidemia (predisposing factors such as hypertension), hypomagnesemia, hyperkalemia, gynecomastia, and hypertrichosis.

Neurotoxicity: There have been reports of convulsions, especially in combination with high-dose methylprednisolone, encephalopathy, anxiety, headache, and fever.

Others: There is an increased risk of developing skin and lymphoproliferative malignancies in cyclosporine-treated psoriasis patients.

- Increase in the occurrence of malignant lymphomas.
- Increase the level of inflammatory cytokines such as TNF-alfa.
- Increase the infection risk.

Administration:

Dosing for Organ Transplant in Adults Oral

- Four to 12 hours pre-transplant: 14 to 18 mg/kg by mouth for one dose.
- One to two weeks post-transplant: 5 to 15 mg/kg per day by mouth divided twice a day.
- Reduce the dose by 5% per week until 5 to 10 mg/kg per day by mouth divided twice per day.

Intravenous (IV) (maximum concentration 2.5 mg/dL)

- Four to 12 hours pre-transplant IV: 5 to 6 mg/kg IV for one dose over 2 to 6 hours.
- Post-transplant until the patient can tolerate oral therapy: 2 to 10 mg/kg IV once per day.
- Adjust dosage according to trough levels.

Focal segmental glomerulosclerosis: Oral 3 mg/kg/day every 12 hours.

Rheumatoid arthritis: Oral (modified), initially: 2.5 mg/kg per day every 12 hrs, increase 0.5 to 0.75 mg/kg per day after eight weeks if the response has not been effective. Maximum dose: 4 mg/kg per day.

Psoriasis: Oral (modified), initially: 2.5 mg/kg per day every 12 hours, increase to 0.5 mg/kg per day after four weeks if the response has not been effective. Maximum dose: 4 mg/kg per day.

Clinical uses:

CyA has been used in small numbers of patients with conditions that may be immunologically mediated.

Routhier and colleagues? gave six patients with primary biliary cirrhosis 5 to 10 mg/kg of CyA daily for 8 weeks. Their serum aspartate aminotransferase and alkaline phosphatase levels fell significantly. The serum levels of CyA were not measured, and the drug was discontinued because of mild rises in the serum creatinine and blood urea nitrogen levels. No follow-up findings were reported.

Mueller and Herrmann? used CyA in four patients with severe psoriasis and found that the skin lesions regressed dramatically approximately I week after the start of CyA therapy but reappeared when the drug was discontinued.

Five patients with systemic lupus erythematosus were treated with CyA by Isenberg and coworkers. The arthralgia of two lessened, but the other patients found no change in their symptoms. The drug was discontinued in all five patients because of side effects (nausea, vomiting, paresthesia, nephrotoxic effects and angioedema). The serum levels of CyA were not monitored.

The incidence of side effects in this series of patients is higher than one would expect from the experience with CyA in transplant recipients and suggests the need for careful regulation of the drug's serum levels.

Uses in Dermatology:

- Sweet's Syndrome:

Sweet's syndrome, pyoderma gangrenosum, and subcorneal pustular dermatosis are neutrophilic conditions that have an inflammatory infiltrate

consisting of mature polymorphonuclear leukocytes. The neutrophils are usually located within the dermis

in Sweet's syndrome and pyoderma gangrenosum, however, in subcorneal pustular dermatosis they are found in the upper layers of the epidermis. Sweet syndrome is also referred to as acute febrile neutrophilic dermatosis. It is a condition of unknown aetiology characterized by pyrexia, elevated neutrophil count, and painful erythematous cutaneous lesions, and usually, prompt clinical improvement is seen following corticosteroid systemic therapy.

The standard therapy for Sweet's syndrome is prednisone or prednisolone at an initial dose of 0.5 mg/kg to 1.5 mg/kg of body weight per day, and gradual reduction is recommended for the following 2 to 4 weeks. Sweet's syndrome can be associated with. other conditions such as Acute Myeloid Leukemia.

The tendency of Sweet's syndrome to relapse was the rationale for trying cyclosporine as a first-line treatment. Several cases have been reported demonstrating the efficacy of cyclosporine for the treatment of Sweet's syndrome.

Cyclosporine had been used in 3 settings: as initial monotherapy, a second-line therapy after the failure of other first-line treatments (steroids) or as a corticosteroid-sparing agent. The initial oral dose has ranged from 2 mg/kg/day to 4 mg/kg/day, to as high as 10 mg/kg/day for the acute presentation; this dose is continued for the first 10 days and then reduced gradually and discontinued at day 21. Patients should be closely monitored due to the side effects.

Cyclosporine has been shown to inhibit neutrophil chemotaxis and, more importantly, impaired neutrophil migration into infective and sterile inflammatory foci in vivo. Monocyte functions are also modulated by cyclosporine and it has been shown in vitro to inhibit antigen presentation and suppress monocyte activation. Even though, Sweet's syndrome is predominantly neutrophilic, inhibition of cytokine release by mature T-helper lymphocytes and decrease of effector found in cytotoxic lymphocytes has been reported. The mode of acting of cyclosporine in this disease may be related to these effects.'

Furthermore, it has been suggested that interleukin 1 (IL-1) might play a key role in Sweet's syndrome. IL-1 possesses endogenous pyrogen activity, is chemotactic to neutrophils, induces neutrophil leucocytosis and stimulates the synthesis of prostaglandin E2.

Cyclosporine has been shown to inhibit the release of II-1.

- **Cyclosporine in Psoriasis:**

Nowadays, even in the age of biologics, cyclosporine remains one of the most effective treatments for psoriasis because of its efficacy and rapid onset of action. Multiple dose-finding studies have been performed to elucidate the optimal dose for cyclosporine that achieves clearance with minimal toxicity. 37 The initial dose of cyclosporine recommended by the American Academy of Dermatology is 2.5 mg per kg daily, administered in two divided doses (every twelve hours). In patients with severe psoriasis, in which a rapid response is needed, an initial dose of 5 mg per kg daily is usually a better option. Although the higher dose is associated with a faster and more efficacious response, it is also associated with a higher rate of adverse reactions. Clinical improvement of the cutaneous lesions occurs after approximately 4 weeks and the maximum response is seen after 8 to 16 weeks. If a satisfactory response is not achieved after 4 to 6 weeks of initial therapy with the lower dose (2.5 mg per kg daily), the dose can be increased gradually by 0.5 to 1.0 mg/kg/day at 2- to 4-week intervals, to a maximum of 5 mg/kg/day, as long as the laboratory parameters remain satisfactory. If the response is still unsatisfactory after 3 months

of treatment with the higher doses, then cyclosporine should be discontinued.

- **Long-Term Therapy:**

Currently, long-term therapy of psoriasis (> 1 year) with cyclosporine is not a common approach and should be prescribed only after other therapeutic options have been considered. This is because of possible adverse effects, including renal toxicity and arterial hypertension.910 There is also the possibility for an Increased risk of developing lymphoproliferative disorders and other malignant tumours, especially squamous cell carcinomas of the skin (more common in patients with high cumulative doses of phototherapy in combination with psoralen-UV-A (PUVA) (>1000 J per cm?). 1,12 Current guidelines limit the continuous use of cyclosporine in the United States to 1 year, 13 whereas in Europe the recommended limit is 2 years.

- **Short-Term Therapy:**

The use of intermittent short-term therapy is currently the most commonly recommended regimen of cyclosporine for the treatment of psoriasis. Patients are treated until an adequate response is achieved, which generally requires 8 to 16 weeks. Subsequently, cyclosporine is discontinued or slowly tapered by 1 mg per kg every week over 4 weeks. A short course of cyclosporine can be used in severe flares of psoriasis because of its rapid onset of action until a better long-term alternative treatment is instituted. This is particularly useful in the treatment of erythrodermic or generalized pustular psoriasis where cyclosporine remains as the treatment of choice despite the new biologic medications.

- **Combination Therapy:**

The goal of combination therapy in psoriasis is to increase the efficacy of the treatments while reducing their toxicities, which is especially important in the case of cyclosporine, as its complications, such as hypertension and nephrotoxicity, are dose-related.

Cyclosporine has been used effectively in combination with multiple topical therapies including topical corticosteroids, vitamin D3 analogues, and anthralin. These combinations are safe and effective as topical therapies improve the response to cyclosporine allowing the reduction of the cyclosporine dose.

In contrast to topical agents, the combination of cyclosporine with phototherapy is more controversial. Although cyclosporine has been combined with ultraviolet B, and PUVA, there is an increased risk of skin cancer (squamous cell carcinomas). Therefore, the combination of these therapeutic modalities should be avoided, whenever possible.

Cyclosporine has also been combined with other systemic therapies such as acitretin, methotrexate, mycophenolate mofetil, and biologics to achieve greater efficacy and safety. Among these, the most extensively studied is the combination of cyclosporine with Biologics and Methotrexate. The use of cyclosporine with metho-treated is controversial because cyclosporine is nephrotoxic DI methotrexate is excreted by the kidneys, methotrexate is hepatotoxic and cyclosporine is metabolized by the liver.

However, several studies using this combination for psoriasis and psoriatic arthritis seem to demonstrate benefits without a significant increase in side effects, at least with a long-term treatment.

The combination with Acitretin has not evidenced additional benefits,45 and in these cases careful monitoring of triglycerides is warranted, as both agents alone can cause hypertriglyceridemia.

This combination may play a role in the treatment of patients with multiple squamous cell carcinomas, as low doses of Acitretin have shown efficacy in preventing recurrences of skin cancer.

The combination with biologics has been discussed extensively in the literature, but the

long-term risks and side effects are not well studied. Opportunistic infections have been reported in patients treated with biologics in conjunction with other systemic immunosuppressive agents. Therefore, it is advisable to minimize the overlap period.

Although not optimal for the treatment of psoriatic arthritis, there is some evidence of benefit with the use of cyclosporine, either alone or in combination with methotrexate.

Adverse Drug Reactions/Safety:

The most frequently reported adverse effects associated with the use of cyclosporine as short-term in dermatology (maximum dose 5 mg per kg) include increases in serum creatinine, increase in blood urea nitrogen, arterial hypertension, decreased magnesium, increased bilirubin, increased liver enzymes, gingival hyperplasia, paresthesias, headache, muscle aches, and generalized hypertrichosis.

Other adverse effects have also been reported in long-term studies including the development of lymphoproliferative disorders and other malignant tumours. However, the majority of these studies did not evaluate the risk in the general population or psoriasis populations and did not evaluate the patients for years after discontinuation of the drug. The largest study (over 1200 subjects) evaluating the long-term safety of cyclosporine in dermatologic patients concluded that there was no evidence that cyclosporine at dermatologic doses (maximum 5 mg/kg/day) with no additional immunosuppression increased the risk of lymphomas or internal malignancies. However, the same study demonstrated a significant increase in the incidence of non-melanoma skin cancers (especially squamous cell carcinomas). Another adverse event associated with long-term treatment is the development of opportunistic infections. Like other immunosuppressive therapies, cyclosporine may increase the risk of various bacterial, parasitic, viral, and fungal infections, as well as the risk of infections with opportunistic pathogens.

Summary:

In our opinion, even with recent developments of new therapeutic modalities, cyclosporine remains an effective systemic therapy for moderate to severe psoriasis. Current American Academy of Dermatology guidelines suggest that intermittent therapy with cyclosporine for psoriasis is preferable to long-term treatment. In long-term therapy, the risks and benefits for each patient must be weighed carefully due to adverse drug reactions, especially nephrotoxicity and increases in blood pressure, as well as a potentially increased risk of non-melanoma skin cancer. In cases in which long-term treatment is needed, the duration of continuous treatment should not exceed 1 year whenever possible.

Side effects:

In general, CyA has had relatively little toxicity when employed alone, especially as clinicians have become more experienced with its use. One of its major advantages compared with conventional immunosuppressives is its lack of myelotoxicity: no episodes of bone marrow suppression due to CyA have yet been described. This is especially significant for bone marrow transplantation, as one does not wish to suppress the newly transplanted marrow. Nephrotoxic effects, both acute and chronic, are among the most common side effects of CyA therapy.'S We feel that both types are usually associated with high serum seals that achieve a cheaper sed by lowering However, we. have had one patient with a gradually rising serum creatinine level who showed no evidence of rejection and whose serum levels of CyA were within the therapeutic range. When CyA was replaced with azathioprine his creatinine level fell immediately. We have interpreted this as an instance of a nephrotoxic reaction to CyA, possibly due to abnormal

sensitivity to the drug or due to the accumulation of nephrotoxic metabolites.

The renal biopsy findings in patients for whom CyA is nephrotoxic may be normal, but they are often indistinguishable from those of mild chronic rejection."8 Mihatsch and collaborators? have reported giant mitochondria in the renal tubular cells of patients receiving CyA who had clinical evidence of a nephrotoxic reaction. However, this finding can also be made in renal transplant patients not receiving CyA. In renal biopsy specimens from three recipients of bone marrow transplants who were thought to have a CyA nephrotoxic reaction, Shulman and associates described glomeruli-lar-capillary thromboses, mesangial sclerosis and severe tubulointerstitial disease. Although these findings are nonspecific, they were not present in other patients not treated with CyA, so they suggest that CyA may be associated with renal endothelial damage leading to microvascular thromboses. It is hoped that with more experience biopsy changes specifically due to CyA toxicity will be recognized.

We must emphasize that nephrotoxic effects are seen in only a minority of patients; most patients can take the drug for long periods without renal impairment. It is not always clear whether a slow rise in the serum creatinine level following renal transplantation is due to chronic rejection or a toxic reaction to CyA, which requires different forms of therapy. We have found that the resolution of this question is greatly aided by the measurement of both the serum level of CyA and the immune response to donor tissue, as judged by the lymphocyte-mediated and complement-dependent cytotoxicity. If there is minimal or no interstitial cellular infiltrate in the biopsy specimen, the serum level of CyA is high, and tests for both types of cytotoxicity give negative results, a toxic reaction to CyA is the most likely diagnosis. Chronic rejection is suggested by a cellular infiltrate with vascular abnormalities (intimal proliferation and degenerative changes) in the biopsy specimen, a normal or low serum level of CyA and laboratory evidence of lymphocyte-mediated or complement-dependent cytotoxicity. In the first situation, we decrease the CyA dose, and in the second we give methylprednisolone intravenously and increase the CyA dose if the serum level is low. The hepatotoxic effects of CyA are dose-dependent and manifest by readily reversible rises in the serum levels of bilirubin, liver enzymes and alkaline phosphatase.' Clinical effects of hepatotoxicity are rarely seen when the serum concentration of CyA is at a therapeutic level, and have not prevented the successful use of CyA in recipients of liver transplants.

Other occasional side effects include a mild tremor, neuropathy, gingival hypertrophy and hirsutism. The list can be severe and embarrassing but is reversible with discontinuation of the drug. It is our initial impression that these patients may be more susceptible to the dermatologic side effects of prednisone, such as acne, than are patients treated with azathioprine. The relative incidence of infection during CyA therapy as compared with conventional therapy is not clear. Most authors, ourselves included, feel that life-threatening bacterial infections are less frequent with CyA therapy, but Sweny and associates" have found the opposite to be the case. Controlled clinical trials are needed to resolve this issue. Thiru and colleagues" reported the development of lymphomas in 3 of 57 patients 4 to 11 months after the start of CyA therapy. All three patients had been given higher doses of CyA than are presently used, and all showed a rise in the titre of antibodies in their serum to the capsid antigen of the Epstein-Barr virus (EBV).

Crawford and coworkers have shown that patients receiving CyA cannot mount a cytotoxic response to EBV-infected cells in vitro. The tumours in Thiru and colleagues' patients likely developed as a result of an impairment in T-cell function that led

to decreased immunologic surveillance and permitted polyclonal proliferation of B-cells and the transformation of an EBV infection into an unlimited lymphoproliferative process.

Altogether only four lymphomas have been reported in 450 patients receiving CyA, an incidence no higher than that seen in transplant patients given other immunosuppressive agents. CyA is not mutagenic in the Ames test' and has not been shown to produce chromosomal abnormalities. Indeed, the fact that the lymphomas occurred in the early post-transplantation period suggests that CyA allowed another agent, such as EBV, to express its oncogenicity. Longer follow-up is needed before the true incidence of lymphomas in patients receiving CyA is known.

CONCLUSION

Although moderate to severe psoriasis remains the only FDA-approved indication for the use of cyclosporine in dermatology, the drug has been used with very good results for the treatment of multiple dermatologic conditions, including atopic dermatitis, neutrophilic dermatoses, connective tissue disorders, and autoimmune bullous diseases among others. In our opinion, cyclosporine plays an essential role in the dermatologic therapeutic arsenal due to its efficacy and rapid onset of action. Furthermore, short-term therapy and low doses translate into fewer side effects. It is also important to note that in dermatology, cyclosporine is frequently used as monotherapy and therefore the rates of complications are seen in a small percentage of patients.

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