

Cyclosporine: the new silver bullet?

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Cyclosporine is the closest thing to the silver bullet that veterinary medicine has seen. Its ability to improve numerous inflammatory diseases combined with the apparent lack of adverse reactions in veterinary species makes cyclosporine close to an ideal treatment.

Key points:

Compared to steroid therapy, cyclosporine is safe and effective.
Do not treat animals with concurrent tumors.
Aggressively treat all secondary infections (skin, UTI, respiratory).
Cyclosporine may be less effective the second time around so use it wisely.
For now, do not use live virus vaccines.

Background:

Cyclosporine is a macrolactam derived from a fungus. It was first used to treat psoriasis in 1979. Other drugs in this family include tacrolimus (Protopic[®] introduced in 2000) and pimecrolimus (Elidel[®] introduced in 2001).

Cyclosporine drugs work by targeting the T lymphocytes binding immunophilin (cyclosporin binds cyclophilin, tacrolimus binds macrophilin) thus inhibiting calcineurin which is needed to stimulate the nuclear factors of activation (NF-ATp) to produce inflammatory cytokines. This precise targeting of the T lymphocytes inhibits the production of the numerous cytokines driving the inflammatory reaction. Unlike systemic steroids that affect every cell in the body producing numerous unwanted effects, cyclosporine only affects inflammatory cells. The T lymphocytes serve as the brains of the entire immune system. Therefore, if you disable the T lymphocytes then the entire inflammatory cascade is suppressed. Due to its precise mechanism of action, the adverse effects of cyclosporine are limited in number and severity.

Cyclosporine also affects Langerhans cells by decreasing their migration into tissues and their ability to process antigen. Mast cell degranulation is reduced releasing less histamine. Keratinocytes are affected and a decrease in IL-9 receptors can be identified.

Cyclosporine is a large molecule that is unable to penetrate the epidermis. Its topical application results in minimal alterations in the cutaneous inflammatory reaction. Newer compounds such as Tacrolimus and pimecrolimus are smaller molecules able to penetrate the epidermis resulting in effective anti-inflammatory topical therapies. Protopic (0.1% Tacrolimus) has revolutionized the treatment of allergic dermatitis in humans.

Cyclosporine has been used to treat numerous diseases in human and in veterinary medicine with variable results.

Allergic Dermatitis	Dermatomyositis	granulomas
Discoid Lupus	Vasculitis	Scleroderma
Pemphigus	Urticaria	Senile pruritus
Bullous pemphigoid	Rheumatoid arthritis	Poison Ivy
Systemic Lupus	Sweet's syndrome	AIHA
Sebaceous Adenitis	Panniculitis	Colitis
Granulomatous dermatoses	Erythema multiforme	Organ Transplants
Psoriasis	Hypereosinophilic syndrome	Androgenic alopecia
Actinic dermatitis	Eosinophilic	Vitiligo
		Ichthyosis
		Mycosis fungoides

Studies before 1995 used formulations of cyclosporine with highly variable oral absorption making interpretations of these clinical trials difficult. Neoral[®] was released in 1995 and utilized a special formulation (microemulsion properties) making oral absorption more consistent and predictable. This provided a reliable cyclosporine product for therapeutic use.

In 2003, Novartis released Atopica[®]. This is the first veterinary specific formulation of cyclosporine that demonstrates consistent oral absorption similar to Neoral. Atopica[®] is available in four capsules sizes (10 mg, 25 mg, 50 mg, and 100 mg).

Canine allergic dermatitis is the most common disorder currently treated with oral cyclosporine therapy. In numerous studies, 5 mg per kilogram per day of cyclosporine results in 70% improvement of clinical symptoms. This response rate is comparable to allergy testing and immunotherapy (allergy vaccines). The cost of cyclosporine therapy makes treating large dogs expensive; however, in smaller patients, the potential response rate and limited adverse effects make cyclosporine therapy an attractive and practical option.

Treating autoimmune skin disease with cyclosporine seems to be less predictable than the treatment of allergic dermatitis. In the author's experience, approximately 50% of patients with a variety of autoimmune skin disorders respond to cyclosporine therapy (SLE, PF, PV, vasculitis, EM, Hypereosinophilic syndrome). Despite this less than ideal response rate, the limited adverse effect profile of cyclosporine treatment compared to immunosuppressive steroids and chemotherapeutic agents make cyclosporine an extremely attractive treatment option for long-term control of autoimmune disorders.

Treatment:

The target dose is usually 5 mg per kilogram per day; however, the addition of drugs that compete with the cytochrome P-450 enzyme system in the liver can increase cyclosporine blood levels by approximately two times (double). This will allow the daily dose to be tapered to every-other-day or the 5 mg per kilogram dose be lowered.

Anecdotal reports suggest that aggressive tapering schedules or discontinuation of cyclosporine therapy may make subsequent treatment attempts unsuccessful in some patients; therefore, owners should be counseled prior to stopping cyclosporine, especially if it is efficacious in their patient.

Cyclosporine is started at the 5 mg per kilogram per day dose. The patient is usually maintained on daily therapy for six to eight weeks or until a beneficial response in the inflammatory condition is observed. Once the patient responds, the cyclosporine dose can be tapered by either decreasing the frequency to every-other-day and possibly every third day or by lowering the dose from 5 mg per kilogram per day to the lowest possible to those that controls the inflammatory condition. Cyclosporine therapy will likely need to be continued for a prolonged period of time especially in chronic inflammatory conditions such as allergy or autoimmune skin disease. The limited adverse effects associated with cyclosporine therapy compared to long-term steroid therapy make cyclosporine a much better treatment option for chronic long-term control of inflammatory disorders.

Ketoconazole (5 to 10 mg per kilogram per day) can be administered concurrently to increase cyclosporine blood levels. In these patients, the dose of cyclosporine can be reduced (approximately half) or possibly tapered sooner than in patients not receiving the combination protocol. The addition of ketoconazole is especially useful in allergic patients with concurrent Malassezia dermatitis or otitis.

Pretreatment survey blood work (CBC, serum chemistries, and urinalysis) is usually performed to identify patients with concurrent renal or liver disease. Generally after the first four to six weeks of cyclosporine therapy, survey blood work is reevaluated to identify any developing problems.

Adverse effects:

The adverse reactions to oral cyclosporine in dogs and cats are very few. Gastrointestinal irritation is the most common reported adverse effect and occurs in approximately 30% of patients (only ap 5% severe enough to discontinue therapy). Gingival hyperplasia and papilloma-like lesions have been reported but are rare occurring in less then 3% of dogs receiving cyclosporine therapy.

In humans, renal complications are common problem associated with cyclosporine treatment. This does not seem to be a problem in our veterinary species.

The risk of secondary bacterial and yeast infections caused by the immunosuppressive effects of cyclosporine are concerning. Interestingly, cyclosporine does not seem to suppress the entire immune system enough to cause a significant increase in secondary infections. Cyclosporine is used to treat disorders that commonly predispose a patient to secondary infections. Controlling these underlying disorders likely reduces the development of new infections more then the immunosuppressive effects of the cyclosporine in increases the risk. Practically, the overall result is a decrease in the rate of secondary infections. Patients may be at risk for developing Papilloma virus infections.

The immunosuppressive effects of cyclosporine may predispose patients to the development of neoplasia. T-cells play an important role in tumor surveillance. Large studies in humans receiving cyclosporine for the long-term control of psoriasis failed to identify a significant increase in the number of neoplastic conditions. Despite this, anecdotal reports in veterinary medicine continue to identify neoplasia during cyclosporine therapy. Whether this is coincidental or due to a suppression of normal tumor surveillance is unclear at this time. Patients with neoplasia should not be treated with cyclosporine.

Cyclosporine likely does not interfere with routine vaccination protocols; however, Novartis currently recommends avoiding live virus vaccines in patients being treated with cyclosporine.

Tacrolimus (excerpt from Veterinary Medicine Aril 2004)

At The University of Tennessee, we have had good success treating perianal fistulas and DLE with topical tacrolimus (Protopic 0.1%—Fujisawa Healthcare) applied twice a day until the lesions resolve then tapered to the lowest frequency that controls the inflammation (usually every 2-3 days).¹ Tacrolimus is a macrolide immunosuppressant that inhibits T-lymphocyte activation. It penetrates the skin better than topical cyclosporine. Tacrolimus costs about \$70 for a 30-g tube, so sticker shock can be a problem. Since only enough ointment is needed to cover the lesions, the 30-g tube usually lasts 1-3 months. Owners should use a cotton tipped applicator or gloves to avoid contacting the ointment. In humans with atopic dermatitis, a mild burning sensation has been reported; however, few veterinary patients demonstrated any adverse reaction.

Summary:

Cyclosporine therapy should be considered as an alternative to steroid treatment in any patient where steroids would be used for prolonged periods of time. The adverse effects of cyclosporine compared to the adverse effect profile of systemic steroids are extremely low. The response rate to systemic cyclosporine therapy is not perfect but given the extremely low adverse effect rates, cyclosporine should be considered as the treatment option for any patient with a chronic inflammatory disease. Tacrolimus offers a topical treatment option that provides an effective treatment option for select focal immune mediated skin diseases.

References available upon request.