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CYCLOSPORINE THERAPY I: IMMUNE MEDIATED DERMATOSES

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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 side effects in veterinary species makes cyclosporine close to an ideal therapy.

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).
• For now, do not use live virus vaccines.

BACKGROUND
Cyclosporine is a macrolide derived from a fungus. Cyclosporine was first used to treat psoriasis in 1979 and finally approved in 1983. 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
Discoid Lupus
Pemphigus
Bullous pemphigoid
Systemic Lupus
Sebaceous Adenitis
Granulomatous dermatoses
Psoriasis
Actinic dermatitis
Dermatomyositis
Vasculitis
Urticaria
Rheumatoid arthritis
Sweet’s syndrome
Panniculitis
Erythema multiforme
Hypereosinophilic syndrome
Eosinophilic granulomas
Scleroderma
Senile puritus
Poison Ivy
AIHA
Colitis
Organ Transplants
Androgenic alopecia
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).

ALLERGY
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 up to an 80% response rate (greater than 50% reduction in 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. Long-range studies suggest that 75% of allergic dogs treated with cyclosporine can be tapered to alternate day dosing following the induction period (6-8 weeks).

PERIANAL FISTULAS
Cyclosporine has proved to be a useful tool in the treatment of PA fistulas. This disorder is now recognized as an aberrant immune response that responds best to medical therapies designed to suppress the immune system. The surgical techniques often used for PA fistulas are now rarely used and reserved for the most refractory cases. The ideal treatment for PA fistulas uses multifaceted medical protocols.
designed to decrease bacterial loads, avoid dietary antigens, and suppress the immune system. Cyclosporine and tacrolimus have provided tremendous benefits to these patients by providing immunosuppressive alternatives to high dose steroidal therapies that lead to iatrogenic Cushing’s disease.

In an attempt to identify and control any underlying disorders, the patient should be screened for hypothyroidism, and food allergy. A broad spectrum antibiotic should be used for 30 days to help eliminate any deep infections complicating the fistular lesions. Topical steroids can provide an inexpensive topical immunosuppressant. The author uses Genesis spray due to its large bottle size and forceful spray nozzle that helps clean the area while administering the topical triamcinolone.

Tacrolimus alone or in combination with topical steroids is highly effective when applied every 12-24 hours. With time, the frequency of application can usually be reduced to every 24-72 hours based on the patient’s response.

Systemic immunosuppression can be achieved by administering high doses of prednisone alone or in combination with cyclosporine. Cyclosporine as a monotherapy maybe highly effective but is expensive in large breed dogs. The author often uses cyclosporine combined with systemic prednisone until the fistulas have improved (usually 4-8 weeks) then the prednisone is tapered and discontinued over a 4-6 week tapering interval. This leaves the patient on cyclosporine and either topical Genesis spray or tacrolimus for long term maintenance. PA fistulas should be considered a controllable disease rather than a curable disease, as long-term maintenance treatments are usually needed.

**AUTOIMMUNE AND IMMUNE-MEDIATED SKIN DISEASES**

Immune-mediated skin diseases (pemphigus, lupus, vasculitis, and drug reactions) are difficult to treat and are often devastating dermatological disease to control. The historic efficacy of cyclosporine varies but response rates are generally low. 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, TEN, and Hypereosinophilic syndrome). Regardless, the author usually includes cyclosporine as one of several immunosuppressive drugs in a patient’s treatment protocol. The benefits of being able to taper the more potent immunosuppressive treatments (steroids and chemotherapeutics) and rely on cyclosporine as a monotherapy, with is relatively low adverse effect profile, make it worth trying.

Most reports evaluating the efficacy of cyclosporine for immune-mediated skin diseases used older formulations with greater variability in their absorption or attempted low dose therapy (5mg/kg/day). More recent reports in human and veterinary medicine evaluated the efficacy of cyclosporine for the treatment of pemphigus demonstrated no benefit from the inclusion of cyclosporine as part of the patient’s immunosuppressive treatment protocol. The newer microemulsified formulations may need to be administered at significantly higher doses to promote remission of autoimmune skin disease like Pemphigus and Lupus.

The author uses oral cyclosporine for moderate to severe cases of autoimmune or immune-mediated skin disease. Atopica is combined with immunosuppressive prednisone and oral antibiotics. In severe cases, azathioprine or chlorambucil is added to the protocol. Topical antimicrobial baths are administered every 3-7 days to assist in the removal of crust and to help prevent secondary cutaneous infections. After 3-4 weeks, the patient is reevaluated and if the lesions are improving the medication are tapered.

The goal is to reduce the dose of prednisone to the lowest level needed to keep the lesions controlled. The author typically slowly tapers the prednisone over a 2-3 month period to prevent recurrence of the skin disease. The goal would be to completely taper and discontinue the prednisone, then reduce and possibly discontinue the azathioprine and possibly the antibiotics leaving the cyclosporine as the monotherapy. Unfortunately, most cases require the continued use of combinations of immunosuppressive therapy.

**TREATMENT PROTOCOL**

Cyclosporine is started at the 5 mg per kilogram per day. 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 dose 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.

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 25-30% of patients (only approximately 5% severe enough to discontinue therapy). Gingival hyperplasia and papilloma-like lesions have been reported but are rare occurring in less than 3% of dogs receiving cyclosporine therapy.

In humans, renal complications and hypertension 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. The latest veterinary data suggests that there is NO increase in neoplasia associated with cyclosporine therapy. 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 April 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). Tacrolimus is a macroline 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 demonstrate 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.