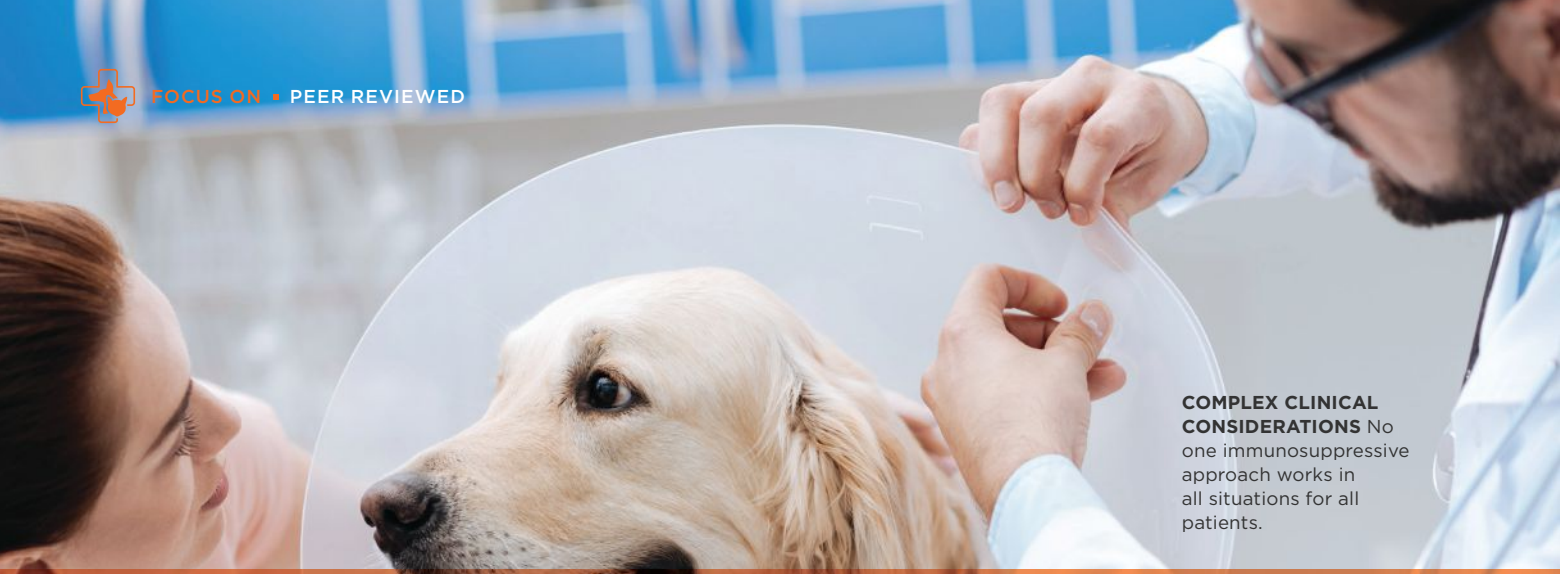

COMPLEX CLINICAL CONSIDERATIONS No one immunosuppressive approach works in all situations for all patients.

FOCUS ON

Oral Cyclosporine Use in Dogs

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Cyclosporine is a potent immunosuppressive agent that has treatment applications in both veterinary and human medicine. It is a cyclic polypeptide derived from the soil fungus *Tolypocladium inflatum*. In 1983, cyclosporine gained U.S. Food and Drug Administration (FDA) approval for the prevention of transplant rejection in humans. In 2003, it was FDA-approved as Atopica (at that time, manufactured by Novartis Animal Health, but now manufactured by Elanco, elanco.com) for treatment of atopic dermatitis in dogs. Oral cyclosporine is currently being used to treat a spectrum of inflammatory and immune-mediated diseases in dogs, including but not limited to atopic dermatitis, autoimmune skin disorders, perianal fistula, inflammatory bowel disease, granulomatous meningoencephalitis, and immune-mediated blood disorders (e.g., immune-mediated hemolytic anemia, pure red cell aplasia, and immune-mediated thrombocytopenia).[1]

MECHANISM OF ACTION

Cyclosporine inhibits the enzyme calcineurin and modulates the adaptive immune system by specifically inhibiting T-cell function. Calcineurin inhibitors such as cyclosporine begin their biological effects by binding to cyclophilin, an intracellular protein; cyclophilin A is the most abundant cyclophilin in T cells. This binding subsequently inhibits calcineurin by inhibition of its phosphatase activity, ultimately decreasing T-cell cytokine gene expression. Although expression of many cytokines can be affected, the most notable cytokine is interleukin (IL)-2. The role of IL-2 in the inflammatory process is complex and multifactorial, involving proinflammatory and regulatory functions. Cyclosporine markedly decreases IL-2 expression in CD4+ type 1 T-helper cells, inhibiting proliferation and activation of T-helper and T-cytotoxic lymphocytes and blunting the immune response.

ORAL FORMULATIONS

The initial oral formulation of cyclosporine for use in humans was Sandimmune (Novartis), a vegetable oil–based preparation. Its absorption varied significantly from patient to patient, and pharmacokinetics differed widely within and among individual patients. As a result, Novartis developed a newer modified formulation and introduced it into the human market in 1996. This newer formulation was ultramicronized, forming a microemulsion after contact with aqueous fluids, and became much more consistently and predictably absorbed. Novartis originally manufactured and marketed the approved human ultramicronized formulation (Neoral) as well as the veterinary use–approved ultramicronized formulation product (Atopica), although Atopica is now marketed by Elanco

(elanco.com). Generic formulations are also available for both formulations of cyclosporine: modified and nonmodified. Although some generic modified formulations have demonstrated bioavailability in dogs similar to that of the FDA-approved product[2] and can be effective for treatment of certain conditions, such as canine atopic dermatitis,[3] only Atopica has undergone extensive pharmacokinetic testing in dogs. We therefore prefer to use Atopica but will consider other modified preparations when cost prevents use of Atopica. Through our experience with thousands of samples submitted to the Pharmacodynamic Laboratory at Mississippi State University from canine patients receiving Atopica as well as generic oral cyclosporine preparations, it is our opinion that approximately comparable clinical results can be achieved from any of these products, provided the cyclosporine used is a modified product. Because many pharmacies advertise generic or compounded cyclosporine preparations for dogs without clarifying the type of preparation, when prescribing cyclosporine from an online or compounding pharmacy, specifically ask if the cyclosporine is modified. When we called pharmacies advertising generic or compounded cyclosporine for dogs, we found that some were selling the Sandimmune version and others were selling the modified version. Because of the poor absorption and extreme variability in bioavailability of the nonultramicronized preparations of cyclosporine, they are not recommended for use in dogs.

CONSIDERATIONS FOR CLINICAL USE

Key pharmacokinetic parameters influencing the clinical use of cyclosporine include decreased absorption when given with food, peaking of blood concentrations about 2 hours after oral administration, metabolism mainly by the liver through the cytochrome P-450 3A enzyme system, and excretion through the biliary system with retention of the drug in the skin and, potentially, the gastrointestinal tract and liver.

Administration with Food

Oral cyclosporine is best administered at least 2 hours before or after ingestion of food.

Administration with Other Drugs

Because the P-450 enzyme system is the key pathway for cyclosporine metabolism, any medication that influences the P-450 3A enzyme has the potential to affect cyclosporine blood concentrations. Ketoconazole has purposefully been given concurrently with cyclosporine to inhibit the P-450 3A enzyme and thus decrease drug metabolism, allowing for a lower and less expensive cyclosporine dosage. When administering other medications in addition to cyclosporine, we recommend checking a drug formulary for possible drug interactions.

Dosing Protocols

Cyclosporine protocols should be individualized according to disease location and severity. Dosages for dogs with chronic, non–life-threatening diseases typically differ from those for dogs with more life-threatening immune-mediated diseases. Cyclosporine dosages for dogs with chronic mild inflammatory diseases, particularly diseases affecting tissues where the drug may be concentrated (e.g., atopy, immune-mediated skin disease, anal furunculosis, mild inflammatory bowel disease, and chronic hepatitis), are often started lower (typically 5 mg/kg PO q24h) and tailored to resolution of clinical signs. For these patients, the main criterion used to determine adequacy of a cyclosporine dosage is response to therapy; therapeutic drug monitoring is typically not recommended. However, measurement of blood drug concentrations or pharmacodynamic monitoring can be considered for dogs with refractory disease or dogs in which secondary infections develop despite low cyclosporine dosages.

Our laboratory has found that pharmacodynamic effects in dogs receiving cyclosporine are similar to those in people; that is, individual responses are highly variable from patient to patient receiving the same oral dose at the same rate. In dogs with life-threatening diseases (e.g., immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, and severe inflammatory bowel disease), the correct cyclosporine dosage for the individual patient must be established as quickly as possible. Initial cyclosporine oral dosing should be twice daily (approximately 5 mg/kg q12h), and therapeutic drug monitoring (either cyclosporine blood concentrations or pharmacodynamic assays) should then be conducted to ensure that the most appropriate dosage is being used for that individual patient. Achieving the correct dosage as soon as possible is paramount for successful outcomes because too high a dose can be cost prohibitive for the client and lead to unwanted and significant side effects for

the patient; too low a dose does not maximize the chances of disease remission and can lead to expensive consequences, such as the need for hospitalization or transfusion. We use pharmacodynamic monitoring in our canine patients with severe disease to help guide therapy and dosage adjustments in the individual dog.

Time to Effect

Pharmacodynamic testing has shown that oral cyclosporine reaches maximal effect by day 3 of oral dosing in healthy dogs and by day 7 in clinically ill patients.[4] Our experience has been that the full therapeutic benefit of cyclosporine is attained after a week of therapy and that additional time at the same dosage will not increase immunosuppression. Thus, before concluding that the current dosage of cyclosporine is ineffective, allow 1 full week of therapy. In contrast, other immunosuppressive medications (e.g., mycophenolate mofetil and azathioprine) seem to take 2 to 3 weeks to reach full therapeutic effect.

Monitoring

Therapeutic drug monitoring in the form of measurement of cyclosporine blood concentrations or pharmacodynamic assays can help individualize therapy.

Blood Concentrations: Measurement of cyclosporine blood concentrations typically involves collecting a peak sample (approximately 2 hours after dosing) and/or a trough sample (just before the next dose is administered). We recommend contacting the laboratory that will be running these samples for recommendations on ideal sample timing and interpretation of results.

Pharmacodynamic Assays: At Mississippi State University, we recommend sending a single peak sample (approximately 2 hours after dosing) for dogs receiving cyclosporine twice daily and both a peak and a trough sample for dogs receiving it once daily. Results from each sample are reported with therapeutic recommendations for the individual patient.

Adverse Effects

Adverse effects associated with administration of cyclosporine are typically minimal with low-dose once-daily therapy (5 mg/kg q24h) and more common at high-dose twice-daily therapy (5 to 10 mg/kg q12h). The most common adverse effects tend to be gastrointestinal (e.g., vomiting, diarrhea, and inappetence/anorexia).[5,6] Much less common adverse reactions include gingival hyperplasia, gingivitis/periodontitis, papillomatosis, hyperkeratosis of the footpads, coat shedding, hirsutism, lethargy, hepatotoxicity, anaphylactic reactions, angioedema, emergence of neoplasia (specifically lymphoma),[7] nephropathy, and tremors.[1,5,6] Strategies to deal with the gastrointestinal adverse effects of cyclosporine therapy include freezing the capsules and administering them frozen (which does not significantly affect cyclosporine pharmacokinetics in dogs[8]) or concurrently administering an anti-emetic such as maropitant. Although secondary infections (e.g., bacterial skin and urinary tract infections and fungal infections) can occur with any immunosuppressive medication, risk for infection is higher with use of the potent immunosuppressant dosages of cyclosporine (e.g., 5 to 10 mg/kg q12h) than other agents.[5,6,9,10] In our experience, infection tends to be most likely when the pharmacodynamic assay documents marked suppression of T-cell function or when cyclosporine is used in combination with 2 or more other immunosuppressive agents. Clients should vigilantly monitor their dog for malaise or any other signs of disease and should contact their veterinarian if they notice any worrisome signs. Veterinarians should then perform a thorough physical examination and follow up with diagnostics as indicated, which could include blood work, imaging, or infectious disease testing if a secondary infection is suspected.

SUMMARY

The appropriate use of immunosuppressive agents can be complex; no single approach works in all situations for all patients. One possible option for immune suppression is cyclosporine, which can be effective for a variety of disorders in dogs. We begin therapy with the veterinary use–approved product Atopica when possible and use generic modified products when Atopica is not a good option for an individual patient. We also typically recommend treatment of non–life-threatening disorders with once-daily cyclosporine and more severe diseases with twice-daily cyclosporine. When treating life-threatening disorders, use of therapeutic drug monitoring (blood drug levels or pharmacodynamic assays) helps ensure that the cyclosporine dosage is appropriate and provides the best chance for disease remission while reducing risk for oversuppression and possible subsequent secondary infection. TVP

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Conflict of Interest

Drs. Archer and Mackin supervise and oversee the Pharmacodynamic Laboratory at Mississippi State University College of Veterinary Medicine. Neither has received financial remuneration for work with the Pharmacodynamic Laboratory.

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