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NEW THERAPIES IN VETERINARY DERMATOLOGY

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We will focus in new drugs with immunomodulatory and immunosuppressing effect: cyclosporine A (CsA), tacrolimus and pimecrolimus—two drugs related to CsA-, imiquimod, interferons and intravenous immunoglobulins

CYCLOSPORINE A (CsA)

CsA was isolated in the 70's from the telluric fungus *Tolypocladium inflatum gans* and rapidly its immunomodulatory and immunosuppressive activity was detected. It has been used for decades in human medicine as immunosuppressive drug. Recently, a specific formulation for use in dogs and cats (Atopica^R) has been marketed all over the world (1).

The mode of action of CsA is complex and multifaceted. CsA acts on many cells but, but its main therapeutic action is on T lymphocytes. CsA induces rapidly reversible immunosuppression by inhibiting the initial antigen triggered activation phase of CD4+ T lymphocytes. This immunosuppression comes from the blocking of the transcription genes encoding several cytokines, in particular IL-2. The absence of IL-2 synthesis prevents the activation and proliferation of T lymphocytes, in addition to the secondary synthesis of other cytokines including IL-4, IFN-gamma and GM-CSF. CsA also has inhibitory effects on eosinophils, mast cells and Langerhans cells, among others.

CsA is absorbed orally, specially in the micro emulsion form that is marketed for veterinary use. However, in dogs, even in the micro emulsion formulation, the absorption is slightly delayed when the drug is given with food. Therefore, it is recommended that the drug is administered 2h before or after feeding. Absorption is limited by P-glycoproteins that act as a drug efflux pump from the intestinal epithelial cells by transporting the drug from the intestinal cell to the lumen.

In dogs and man, the drug is metabolised mainly in liver and intestines. The cytochrome P450 is involved in both intestinal and hepatic metabolism. Elimination of CsA is mainly biliary with minimal renal excretion in all species. The unchanged fraction of CsA eliminated by the kidneys is only 1-6%. Ketoconazol, which inhibits cytochrome P450, increases the bio-availability of CsA. If the patient receives a dose of ketoconazol of 5mg/kg/day, the dose of CsA can be halved, with the same effects.

At present time the main indication of CsA in veterinary dermatology is the treatment of canine atopic dermatitis. Several controlled randomised studies have demonstrated its efficacy and safety. The drug is administered at a dosage of 5 mg/kg/24h for 4 weeks. Then, if the patient shows an improvement of 50% or higher of the clinical signs, the dosage is reduced to 5mg/kg/48h and later to 5mg/kg/twice a week. The main side effect is vomiting, which affects 20% of dogs, although in most cases is transient and treatment can be maintained. Diarrhea, gingival hyperplasia, hirsutism and papillomatosis has also been reported.

CsA has also been used to treat perianal fistulas, granulomatous sebaceous adenitis, generalized idiopathic sterile nodular panniculitis and some autoimmune dermatosis.

Furthermore, in cats, CsA has been demonstrated to be effective in the treatment of eosinophilic granuloma complex and plasma cell pododermatitis.

TACROLIMUS

Tacrolimus is a 23 member macrolide produced by *Streptomyces tsukubaensis*, it is available in an oral formulation used extensively as an immunosuppressive in human transplants that has very similar actions to cyclosporine. Side effects preclude this form the use in dogs and cats. ProtopicR is a topical formulation available as a 0.1% ointment. Protopic has topical anti inflammatory effects without the atrophogenic effects and metabolic effects of topical GC's. It was used recently for the treatment of atopic dermatitis in humans and is also beneficial in psoriasis and possibly alopecia areata. Large multicenter human studies indicate it is a very safe drug with minimal systemic absorption. Its mechanism of action is similar to cyclosporine but 10 to 100 times more potent. It works by calcineurin inhibition, resulting in suppression of antigen presenting T cells, inhibition of the production of multiple cytokines from T cells (IL-2, IL-3, IL-4, IFN γ , GMCSF, and TNF-alpha), down regulates cytokine expression in other cells including mast cells, basophils, eosinophils, keratinocytes and Langerhans cells.

It has been reported effective in canine perianal fistula though at a lower rate than systemic cyclosporine, but has been used once there is significant response to cyclosporine for the final therapy or maintenance of perianal fistula therapy. It appears to have some efficacy in atopic diseases and other possible indications with localized lesions associated with discoid lupus erythematosus, pemphigus erythematosus, pemphigus foliaceus. Anecdotal reports describe its use for a wide number of veterinary dermatologic diseases.

PIMECROLIMUS

Pimecrolimus (ElidelTM) is an ascomycin macrolactam derivative that acts similarly to tacrolimus. It is used similarly to ProtopicTM though has had less of an irritant effect in some cases. No comparisons have been done in dogs but anecdotal reports have suggested similar or lower efficacy than Tacrolimus.

IMIQUIMOD

Imiquimod (AldaraTM) is an exciting drug as it is topically applied, has few side effects, and appears to stimulate natural immune function. Therefore it is being tried on a wide variety of human diseases and will undoubtedly find more uses in veterinary medicine as well. Diseases recently reported in human dermatologic therapy include: decreasing recurrent rates of keloids, other viral induced warts, and molluscum contagiosum (human pox-virus), and epithelial premalignant or neoplastic diseases such as squamous cell carcinoma. These observations suggest it may be a valuable therapy for a variety of cutaneous viral lesions but also epithelial diseases seen in cats, particularly actinic keratosis and squamous cell carcinoma and Bowens disease. For most diseases it is applied at two to three time a week for various intervals and burning or irritant reactions are the major side effects.

Imiquimod had been used successfully, but in uncontrolled situations, to treat two forms of canine papilloma virus, feline herpes, feline papillomas, feline Bowens disease, and equine sarcoids. Serious side effects so far have not been

recognized. The drug may be helpful for solar dermatitis and precancerous solar induced lesions in dogs and cats if lesions are localized. Irritancy may be a problem and seems to be an individual response with horses and cats seemingly more sensitive than dogs. It is applied topically 2-4 consecutive days weekly.

INTRAVENOUS IMMUNOGLOBULINS

This is a relatively new therapy being utilized in the treatment of human immune mediated dermatologic diseases. The exact mechanism of this therapy is unknown, although proposed mechanisms include blockade of Fc receptors, elimination of plasma immune complexes, anti-idiotypic suppression of autoantibodies, inhibition of complement-mediated damage, alterations in cytokine levels (especially transforming growth factor beta, IL-10 and IL-1). Its use has been restricted primarily because of its expense, limited supply of the immunoglobulin, and the requirement for hospitalization to administer therapy. However the long-term remissions and possible cure rate make this an option to be further investigated. The best-studied indications include pemphigus vulgaris and foliaceus, bullous pemphigoid, dermatomyositis, toxic epidermal necrolysis, atopic dermatitis and chronic urticaria. There are also reports of its effective use in many other dermatologic disorders such as other forms of pemphigoid, cutaneous and systemic lupus, scleroderma, and epidermolysis bullosa acquisita. The treatment protocol in these reports varies, but at the high end is 2 gram/kg divided and given over three days then repeated every four weeks until healed, then taper out the therapy.

In veterinary medicine, reports are very limited with the most studied indication being therapy of immune mediated hemolytic anemia, where two separate case series showed limited evidence for its efficacy. It was also used to successfully treat a cat with severe erythema multiforme that was most likely drug induced. Other anecdotal favorable responses have been described for canine erythema multiforme. Short-term responses have been anecdotally seen in feline atopic dermatitis and pemphigus foliaceus.

INTERFERONS

Interferons (INF) are a group of glycoprotein cytokines produced by a variety of inflammatory cells and fibroblasts that have numerous immunologic effects. There are several recognized interferons and they vary in their immunologic effects. The main uses are based on antiviral and antineoplastic properties but they may also be beneficial in a variety of other dermatologic disorders. The initial commercial form of interferon was the recombinant human INF alpha-2b (Roferon-A™) and more recently a veterinary product became available. The recombinant feline INF-omega (Virbagen Omega™) has been shown effective in canine parvoviral infection. All veterinary dermatologic uses are based solely on anecdotal information, although recently two pilot studies have suggested some efficacy.

Uses described in veterinary dermatology are: viral papillomas, recurrent pyoderma, mycosis fungoides, and most recently a pilot study by Carlotti suggest efficacy of Virbagen for atopic dermatitis. The most exciting use utilizes low dose oral therapy which makes the treatment reasonably priced.

The high potency Roferon has been used for canine papilloma virus but also has been evaluated in a pilot study for recurrent pyoderma (Thompson, Grieshaber et al. 2004). This study did not definitively prove efficacy but suggests there may be some benefit. Feline herpesvirus, idiopathic facial dermatitis, atopic and eosinophilic ulcers may also respond to low dose oral therapy.

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