The use of ciclosporin in canine and feline dermatology: Part 1

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INTRODUCTION

Ciclosporin (CsA) has potent immunosuppressive and immunomodulatory activity that has been exploited in human medicine to prevent organ transplant rejection and to manage atopic dermatitis and psoriasis (Arkhaven & Rudikoff, 2003; Dunn et al., 1990; Ellis *et al.*, 1986). Over the past ten years it has become more frequently employed in veterinary dermatology and its value in the management of canine atopic dermatitis (Guaguere *et al.*, 2004; Steffan *et al.*, 2006) and perianal fistulae (Hardie *et al.*, 2005; Patricelli *et al.*, 2002) is now well established. Although licensed for use only in dogs it has also been increasingly employed in the management of feline dermatoses such as atopy and the eosinophilic granuloma complex (Noli & Scarampella, 2006; Vercelli *et al.*, 2006; Wisselink & Willemse, 2009). Attempts have also been made to exploit the anti-inflammatory and immuno-suppressive activity of CsA in the treatment of several other cutaneous diseases of dogs and cats but with inconsistent results.

Although CsA has a wide safety margin in dogs and cats, its administration can have potentially serious side-effects. The purpose of this series of articles is to encourage the judicious use of CsA. This first article will provide a summary of the anti-inflammatory and immunosuppressive activity of CsA, its formulations, absorption and metabolism and its possible side effects. The second article will deal with the use of CsA in canine and feline dermatology, including recommendations on dosage protocols and withdrawal. In addition, possible treatment protocols for specific skin conditions will be discussed.

PHARMACOLOGICAL ACTIONS OF CICLOSPORIN

Ciclosporin (CsA) is a cyclic lipophilic oligopeptide macrolide that diffuses freely across cell membranes. It has immunosuppressive and anti-inflammatory activity but is employed in veterinary dermatology mainly for its immunomodulatory, anti-allergic effects, which are critical in controlling pruritus. These activities are mediated principally by targeting calcineurin-dependent transcription factors (TFs) and, to a lesser extent, other calcineurin-independent TFs and also through non-genomic mechanisms (Ho *et al.*, 1996; Matsuda & Koyasu, 2000; Schreiber & Crabtree, 1992).

Immunosuppressive and immunomodulatory activity

CsA achieves its immunosuppressive activity principally by forming a complex with cytophilin 1, an intracellular receptor. This complex binds to calcineurin phosphatase, inhibiting the activation of specific transcription factors and their translocation to the nucleus (Schreiber & Crabtree, 1992). As a result, CsA prevents the induction of several genes encoding cytokines and their receptors that are involved in the immune response. The principal cells affected are discussed below.

T-cells

One transcription factor, the nuclear factor of activated T-cells (NF-AT), is particularly sensitive to inactivation by CsA and is pivotal in the antigen-induced synthesis of interleukin-2 (IL-2) by T-cells and the expression of the IL-2 receptor on T-cells (Freeman, 1991; Schreiber & Crabtree, 1992). IL-2 plays a critical role in the activation and proliferation of T-cells.

This dual action of CsA, reduced production of and responsiveness to IL-2, selectively suppresses T-cells and consequently synthesis of T-cell cytokines such as IL-4, -5, -6, -8, -13, granulocyte macrophage colony cell stimulating factor (GM-CSF), tumour necrosis factor (TNF)-α and interferon (IFN-γ) (Bunikowski *et al.*, 2001; Ho *et al.*, 1996; Matsuda & Koyasu, 2000).

Suppression of cytokine expression modulates activity of diverse cells, such as T helper dependent B cells, antigen-presenting cells, mast cells, basophils and eosinophils, that are involved in allergic and inflammatory responses.

Antigen presenting cells

CsA reduces numbers and effectiveness of antigen/allergen presenting cells such as Langerhans cells (Bussmann *et al.*, 2009).

B cells

CsA inhibits growth and activity of B cells (Bruner, 2006) but currently there is no evidence that it alters IgA, IgG, IgM or IgE production in dogs (Brazis *et al.*, 2006; Clarke *et al.*, 2003; Takaori *et al.*, 1992) or adversely affects the humoral response to vaccination (Guaguere *et al.*, 2004).

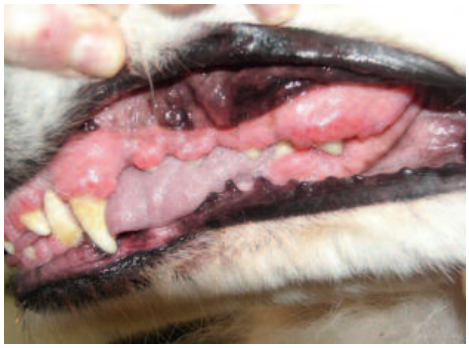

Fig. 1a: *Gingival hyperplasia - German Shepherd Dog on treatment with ciclosporin (5 mg/kg q 24h).*

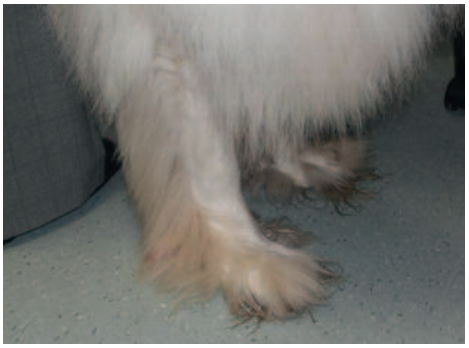

Fig. 2a: *Hypertrichosis - German Shepherd Dog on treatment with ciclosporin (5mg/kg q 24h).*

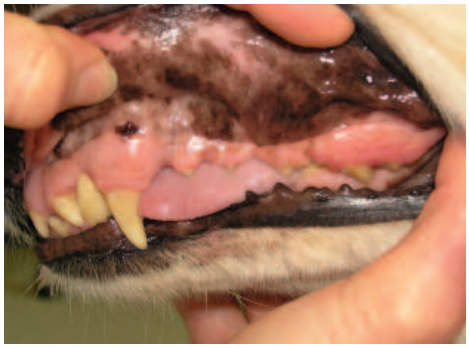

Fig. 1b: *Gingival hyperplasia - German Shepherd Dog six months after treatment with ciclosporin was withdrawn.*

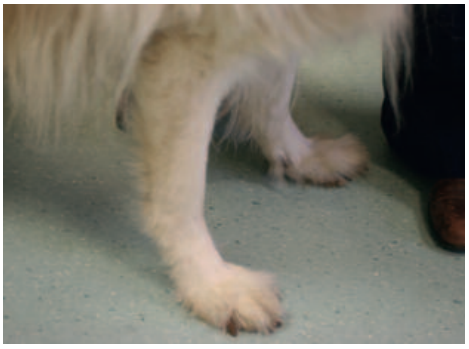

Fig. 2b: *Hypertrichosis - German Shepherd Dog six months after treatment with ciclosporin was withdrawn.*

TABLE 4: Effects of CsA on haematology, biochemistry and urinalysis of dogs

Factor	Parameter	Reported Effect
Haematology	RBC count	Slight increase
	WBC, lymphocytes, eosinophils	Increases and decreases
Biochemistry - blood	Alk Phos	Increase and decrease
	ALT	Increase and decrease
	Glucose	No significant change
	Cholesterol	Increased concentrations
	Urea and Creatinine	Increase and decrease
	Electrolytes	Reduction in Ca++
Biochemistry - serum proteins	Albumin	Reduced concentration
	Gamma globulins	Increased concentration
Urinalysis	-	Bacteriuria and increased WBC count

TABLE 5: Effects of CsA on haematology and biochemistry of cats

Factor	Reported effect
Haematology	No significant change
Biochemistry	Most studies report no significant changes
	Significant reduction in alanine aminotransferase has been reported but values remained in normal range
	Increased creatinine has been reported

Toxicity

In dogs, there is no convincing evidence that CsA is associated with hepatotoxicity, nephrotoxicity or increased risk of lymphoma (Guaguere *et al*., 2004).

Toxoplasmosis

In cats, there is an increased risk of toxoplasmosis (Last *et al*., 2004), possibly viral infections and possibly the development of lymphoma in FeLV positive cats.

Haematology and biochemistry

In dogs (Table 4) the red blood cell count and haemoglobin concentration may be increased but there is no consistent pattern of change in total white blood cell count or neutrophil, lymphocyte and eosinophil counts. Changes in blood biochemistry and serum proteins are inconsistent but all parameters usually remain within their normal ranges.