Treatment of canine atopic dermatitis with cyclosporine: a pilot clinical study

J. FONTAINE, T. OLIVRY

BECAUSE of its unique immunomodulating properties, cyclosporin A has been used to treat various dermatological diseases (Groisser and others 1991, Korstanje and van de Staak 1991). At a daily dosage of 5 mg/kg, cyclosporin A alleviates clinical signs of atopic dermatitis in human beings and causes a 50 to 80 per cent reduction of lesional and pruritus scores (Gaig and others 1993, Ross and others 1993, Stephens and others 1994, Salek and others 1996, Zaki and others 1996).

Because of the similarity which exists between the immunological findings of atopic dermatitis in people and dogs, a study was designed to test the hypothesis that cyclosporin A monotherapy should prove helpful in controlling the clinical signs of atopic dermatitis in the canine species.

Fourteen dogs with chronic non-seasonal atopic dermatitis were selected. In each dog, the diagnosis of atopic dermatitis was made by the fulfillment of Willemse's clinical criteria (Willemse 1986) and exclusion of resembling pruritic dermatoses. Specifically, the dogs' lesions had to have failed to respond to a homemade or commercial elimination diet lasting at least two months. The dogs were considered to be free of cutaneous bacterial or yeast infections because of an absence of compatible clinical signs, or because of lack of response to appropriate courses of antibiotic or antifungal drugs.

This pilot study was designed as an open uncontrolled trial. All dogs were treated with cyclosporin A (Neoral Sandimmun: Novartis-Pharma) at a dose rate of 5 mg/kg orally, once daily for two weeks. The drug was administered, without food, using either 10 or 25 capsules or a 100 mg/ml oral solution to adjust the dose to the target dosage. Other than routine monthly flea control medication and weekly non-medicated shampoos, antipruritic drugs were not allowed.

To quantify the severity of clinical signs of atopic dermatitis in the dogs, a subjective scoring system was developed. Pruritus was estimated subjectively by the owner, on a scale of 0 to 3 (0 none, 1 mild, 2 moderate or 3 severe) to give a 'pruritus score'. Similarly, the extent and severity of the skin lesions were estimated by a dermatologist using a subjective scale of 0 to 5 to give a 'lesional score'. The pruritus and lesional scores were added together to give a 'total score'. The owners were requested, additionally, to provide their subjective perception on the efficacy of cyclosporin A in terms of excellent, good, fair or poor control of the clinical signs of atopic dermatitis.

Pre- and post-treatment pruritus and lesional scores were compared by means of a two-tailed non-parametric repeated measures Wilcoxon signed-rank *t* test using a statistical software package (Prism; GraphPad software). The level of significance was chosen at $P < 0.05$.

Only in one of the 14 dogs in this study did the clinical signs of atopic dermatitis fail to respond to cyclosporin A monotherapy. In all other patients, pruritus, lesional and total scores decreased markedly during this trial (Table 1). Post-treatment scores were significantly different from pretreatment ones ($P < 0.002$). The median reductions of pruritus, lesional and total scores were 100, 60 and 75 per cent, respec-

TABLE 1: Median (95 per cent confidence interval) clinical scores and improvement for 14 dogs undergoing cyclosporin A monotherapy

Score	Before treatment	After treatment	P	Percentage reduction
Pruritus	3.0 (3.0-3.0)	0 (0.0-1.0)	0.0002	100 (68-100)
Lesional	3.5 (2.3-4.2)	1.0 (0.7-2.1)	0.002	60 (30-73)
Total	6.5 (5.3-7.2)	1.0 (0.7-3.1)	0.0002	85 (56-88)

tively. The owners perceived the efficacy of cyclosporin A to be excellent in nine dogs (64 per cent), good in three dogs (22 per cent), fair in one dog (7 per cent) and poor in one dog (7 per cent).

During this trial, severe adverse drug reactions were not observed. Minor side effects, however, were noticed, as vomiting occurred in two dogs after cyclosporin A administration.

The magnitude of reduction of clinical signs observed in this pilot study was identical to that seen in human patients with atopic dermatitis after cyclosporin A monotherapy. Assessment of the response to cyclosporin A administration was made after two weeks, which was similar to the proposal for the treatment of atopic dermatitis in human beings (Grandlund and others 1995, Atakan and Erdem 1998). In this pilot study, the decrease in pruritus scores was greater than for the lesional ones (60 per cent). This smaller decrease in the severity of the dermatitis could be due to the short duration of the trial, as chronic skin lesions probably did not have the time to abate. Ongoing studies have shown that the reduction of clinical scores is higher if the drug is administered for longer periods of time (J. Fontaine, T. Olivry, unpublished observations).

In this study, the tolerance to cyclosporin A was very good. Only minor adverse effects, for example, vomiting, were observed in two dogs. Gastrointestinal symptoms have also been described in people (Atakan and Erdem 1998) and canine patients treated with cyclosporin A (Ryffel 1992). In man, cyclosporin A administration is commonly followed by the development of frequent adverse reactions, such as renal failure and an increase in blood pressure (Grossman and others 1996). In dogs, however, long-term toxicological studies have failed to demonstrate similar severe adverse reactions (Ryffel 1992).

In conclusion, cyclosporin A monotherapy proved very beneficial for 13 of the 14 dogs in this short-term pilot study. Side effects were minor and inconstant. In spite of the non-blinded and uncontrolled design of this experimental trial, it is suggested that the marked reduction in clinical signs, as well as chronicity of the skin lesions, preclude the assumption that the benefit was merely due to a subjective placebo effect. Indeed, the short duration of this trial would most likely prevent atopic lesions from resolving spontaneously due to a seasonal variation in allergen load. Nevertheless, recommendation of cyclosporin A monotherapy for canine atopic dermatitis awaits the confirmation of its efficacy in controlled and blinded trials.

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Veterinary Record (2001) **148**, 662-663

J. Fontaine, DrMedVet, DipECVD, Clinique Vétérinaire, Avenue Brugmann, 425, B-1180 Brussels, Belgium
T. Olivry, DrVet, PhD, DipACVD, DipECVD, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA

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Report on 31 caseous lymphadenitis infected sheep farms in England and Wales

P. J. WATSON, B. E. PREECE

CASEOUS lymphadenitis (CLA) is caused by *Corynebacterium pseudotuberculosis*. There are two distinct biotypes of *C. pseudotuberculosis* – biotype 1 of ovine origin, and biotype 2 of bovine origin. Biotype 1 infects sheep and goats to cause CLA, and biotype 2 infects horses to cause ulcerative lymphangitis, mastitis and abortion, and cattle to cause visceral lesions and mastitis. Natural cross-infection of species by the different biotypes is not thought to occur (Brown and Olander 1987). Although human infection is considered to be rare, several cases associated with occupational exposure have been reported in Australia (Peel and others 1997).

CLA is a chronic disease characterised by suppurative inflammation, most commonly affecting subcutaneous tissue and associated lymph nodes (Brown and Olander 1987). However, abscesses can occur in internal organs and lymph nodes, particularly the lung. In contrast to goats, internal abscesses are not uncommon in sheep. Treatment is not effective at eliminating the organism from infected animals. Ruptured external abscesses and respiratory discharges are considered important sources of infection (Ellis and others 1987). Since *C. pseudotuberculosis* can persist for long periods in the environment (Augustine and Renshaw 1982), envi-

ronmental contamination of sheep sheds is also considered to be a risk factor.

In the UK, in the absence of epidemiological studies, close confinement and increased sheep contact, and possibly shearing and dipping are considered important factors in facilitating the spread of infection within a flock. Affected or subclinical carrier sheep are responsible for the within-flock, and flock-to-flock spread of infection. Contaminated shearing or other equipment could also potentially transmit infection.

CLA is endemic in most sheep-producing countries throughout the world. In some countries the incidence of infection is high and the disease causes considerable economic loss, chiefly at slaughter through carcase condemnation. Control of the disease has proved problematic. Although serology has proven useful in eradication programmes for goats (Dercksen and others 1996), the same has not been true for sheep. Despite the development of a variety of serological tests, none has yet been shown to have high specificity or sensitivity for detecting individual subclinical carrier sheep. Commercial vaccines used in other countries have proven very effective at reducing the number of clinical cases (Paton 1997), but are currently not available in the UK.

CLA was diagnosed for the first time in the UK in 1990 (Lloyd and others 1990). The initial cases were seen in dairy goats which had been in contact with Boer goats imported from Germany in 1987; tracing of imported goats led to further diagnoses. Movement restrictions were placed on infected farms using the Movement of Animals (Restrictions) Order 1990. Consideration was given to making CLA a notifiable disease; however, following the diagnosis of CLA in a sheep flock with no apparent link to imported animals, movement restrictions on infected farms were lifted in 1991 (Robins 1991). Since then, veterinary investigation diagnosis analysis data show a year-on-year increase in the number of diagnoses of CLA from 1992 to 1998; however, no prevalence studies have been conducted in the UK.

In order to gain more information on the extent of CLA infection in England and Wales, articles and letters were published in the veterinary and farming press highlighting CLA as a disease and promoting a free bacteriological screening service by the Veterinary Laboratories Agency (VLA) for suspect cases. A similar service was also offered by the Scottish Agricultural College Veterinary Service in Scotland. This service ran from January 1, 1998, to December 31, 1998.

During 1998, 36 CLA-infected farms were identified, mainly as a result of samples submitted for bacterial screening, although four of these were identified following routine diagnostic postmortem examinations. Where CLA was identified in a flock, permission was sought from the flock owner for a farm visit to be carried out, in order to examine the other animals and to obtain epidemiological information. Where other affected animals were identified at the visit, further samples were collected for bacterial examination and serum samples were stored. All isolates of *C. pseudotuberculosis* have been retained in the VLA bacteriological bead collection. Using a standard protocol, epidemiological information was collected about the clinical history of the flock including the age, sex and origin of the first suspected case and, where present, subsequently affected animals. Information on the farm replacement policy and flock management was also collected as part of the protocol.

A total of 29 farms were visited (28 sheep flocks, one goat herd) by 16 veterinary investigation officers of the VLA. Three farms agreed to provide epidemiological information by telephone only and four farms were unable to accommodate visits for a variety of reasons. The information collected from the 31 sheep flocks is summarised in Table 1.

In addition, abscessed lymph nodes from material condemned at abattoirs was forwarded to the VLA for laboratory

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P. J. Watson, BVM&S, MSc,
CertSHP, MRCVS,
VLA – Penrith,
Merrythought,
Calthwaite, Penrith,
Cumbria CA11 9RR
B. E. Preece, BVSc,
MRCVS, VLA – Starcross,
Staplake Mount,
Starcross, Exeter,
Devon EX6 8PE