Treatment of canine atopic dermatitis with azathioprine: a pilot study

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AZATHIOPRINE (AZA) is an antimetabolite chemotherapy drug that has been used recently for the successful treatment of human beings, both adults and children, with atopic dermatitis, a non-contagious but itchy inflammation of the skin (Meggit and Reynolds 2001, Berth-Jones and others 2002, Meagher and others 2002, Murphy and Atherton 2003, Malthieu and others 2005). This short communication describes an open, uncontrolled trial designed to test whether AZA monotherapy is safe and effective for the short-term treatment of canine atopic dermatitis.

Twelve dogs (eight male, four female) of 12 different breeds, aged between one and eight years old (mean three-and-a-half years), were included in the trial. All of the dogs were diagnosed with non-seasonal atopic dermatitis according to standard methods (DeBoer and Hillier 2001). Oral glucocorticoids and cyclosporine were withdrawn from treatment for at least four weeks and long-lasting injectable glucocorticoids for eight weeks before the trial. All of the dogs were treated solely with 2 to 2.5 mg/kg (mean 2.2 mg/kg) AZA (Imurek; Glaxosmithkline), once daily for eight weeks. Skin lesions were graded at weeks 0, 2, 4 and 8 using the third version of the Canine Atopic Dermatitis Extent and Severity Index (CADESI) (Olivry and others 2007), the version recently validated by the International Task Force on Canine Atopic Dermatitis. At each visit, owners were asked to estimate the level of pruritus by drawing a mark on a 10 cm visual analogue scale. At the end of the treatment (or earlier for dogs withdrawn from the study) investigators and owners together evaluated the efficacy of AZA therapy as 'none', 'poor', 'fair', 'good' or 'excellent'. At each visit, owners were asked to report any side effects of the drug. Complete blood counts and the activity of serum alkaline phosphatase (AP) and alanine aminotransferase (ALAT) were monitored after two, four and eight weeks.

Seven dogs completed the study. Two subjects were withdrawn at the owners' request because of lack of improvement in signs of atopic dermatitis (dogs 2 and 4), and AZA was discontinued in three further dogs because of unacceptable side effects (dogs 3, 7 and 12). In two dogs (dogs 1 and 5), both CADESI and pruritus scores substantially decreased during the eight weeks of AZA administration (Table 1). In both dogs, the efficacy was rated as 'excellent'. In five dogs (dogs 6 and 8 to 11), CADESI and/or pruritus scores declined from baseline by less than 50 per cent, and the efficacy of the treatment was rated as 'fair'. Finally, in one dog (dog 7), scores decreased within two weeks of AZA administration, but side effects developed and AZA was discontinued (efficacy was rated as 'good').

In six dogs, low-level elevations of liver enzyme activity were uncovered at the start of the study (Table 2). This is likely to reflect previous glucocorticoid administration. Following AZA intake, the activity of AP or ALAT rose above normal in 10 of the 12 dogs (83 per cent). Clinical signs suggestive of liver disease motivated the withdrawal of three dogs, all with high AP and ALAT activity. All dogs recovered uneventfully without any treatment other than discontinuation of AZA administration. In the other seven dogs with elevated liver enzyme activity, there were no signs suggestive of liver damage. Mild lymphopenia was observed in three dogs, but anaemia and neutropenia were not uncovered in any of the dogs.

TABLE 1: Clinical efficacy of azathioprine in 12 dogs with atopic dermatitis, shown as a change from baseline in the Canine Atopic Dermatitis Extent and Severity Index (CADESI) and pruritus scores, and as an overall assessment by owners and investigators

Dog	Dose (mg/kg)	Score	Week				Change of score*		Overall assessment
			0	2	4	8	Points	%	
1	2.0	CADESI	52	25	20	16	-36	-69	Excellent
		Pruritus	5	3	2	2	-3	-60	
2	2.1	CADESI	67	62	83	WD	NA	NA	None
		Pruritus	7	8	8	WD	NA	NA	
3	2.3	CADESI	145	146	WD	WD	NA	NA	None
		Pruritus	7	8	WD	WD	NA	NA	
4	2.5	CADESI	85	160	WD	WD	NA	NA	None
		Pruritus	3	9	WD	WD	NA	NA	
5	2.4	CADESI	75	56	32	15	-60	-80	Excellent
		Pruritus	6	4	3	1	-5	-83	
6	2.5	CADESI	38	33	38	24	-14	-37	Fair
		Pruritus	4	3	5	2	-2	-50	
7	2.3	CADESI	53	25	WD	WD	NA	NA	Good
		Pruritus	6	2	WD	WD	NA	NA	
8	2.1	CADESI	58	75	50	45	-13	-22	Fair
		Pruritus	4	8	4	4	0	0	
9	2.1	CADESI	43	45	35	31	-12	-28	Fair
		Pruritus	5	5	5	5	0	0	
10	2.1	CADESI	67	54	32	45	-22	-33	Fair
		Pruritus	6	5	2	4	-2	-33	
11	2.3	CADESI	54	35	33	30	-24	-44	Fair
		Pruritus	7	5	5	4	-3	-43	
12	2.1	CADESI	89	112	WD	WD	NA	NA	None
		Pruritus	8	10	WD	WD	NA	NA	

* From baseline

WD Withdrawn, NA Not applicable

In the present study, the administration of AZA, at a dosage of 2 to 2.5 mg/kg once daily for up to eight weeks, appeared to be effective and safe for the treatment of canine atopic dermatitis in only two of 12 dogs (17 per cent). In five of the dogs the improvements in signs was fair (less than 50 per cent reduction in scores). However, a reduction in clinical scores was noted at the first re-evaluation visit after two weeks in six dogs, suggesting that the pharmacodynamic action of AZA in dogs may be seen earlier than previously perceived (Plumb 2002). Overall, the efficacy of AZA monotherapy appears to be markedly lower than that of the two drugs with proven efficacy for the treatment of this disease (Olivry and Mueller 2003). Treatment of canine atopic dermatitis with oral glucocorticoids or cyclosporine for four to six weeks results in a halving of lesional scores in more than 50 per cent of the dogs treated (Olivry and Mueller 2003). Importantly, this pilot study, in which AZA was used without the concurrent administration of glucocorticoids, resulted in elevations of AP and/or ALAT in nearly all of the dogs treated (10 of 12). In three (30 per cent) of these dogs, there were concurrent clinical signs suggestive of liver damage.

AZA monotherapy, at the dosage used in the present study, has insufficient efficacy and too high a risk to recommend its general use for the treatment of atopic dermatitis in dogs.

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TABLE 2: Side effects of azathioprine therapy in 12 dogs with atopic dermatitis, after eight weeks of treatment

Dog	Dose (mg/kg)	Parameter	0	Week*			Reasons for withdrawal
				2	4	8	
1	2.0	AP	55	384	121	80	No improvement
		ALAT	166	782	128	104	
		Lymphocytes	1.85	1.49	1.76	1.74	
2	2.1	AP	92	865	518	NA	No improvement
		ALAT	27	259	124	NA	
		Lymphocytes	1.37	1.13	1.66	NA	
3	2.3	AP	117	381	NA	NA	Vomiting, anorexia, lethargy
		ALAT	52	720	NA	NA	
		Lymphocytes	1.64	1.25	NA	NA	
4	2.5	AP	28	363	NA	NA	No improvement, pyoderma
		ALAT	46	1108	NA	NA	
		Lymphocytes	1.72	2.14	NA	NA	
5	2.4	AP	32	123	65	66	
		ALAT	54	75	97	70	
		Lymphocytes	2.60	2.40	1.10	1.00	
6	2.5	AP	78	198	154	176	
		ALAT	98	145	354	344	
		Lymphocytes	3.30	3.10	1.70	1.30	
7	2.3	AP	31	154	NA	NA	Lethargy, jaundice, anorexia
		ALAT	23	650	NA	NA	
		Lymphocytes	2.10	1.20	NA	NA	
8	2.1	AP	32	156	67	198	
		ALAT	43	134	145	123	
		Lymphocytes	1.8	1.7	1.3	1.9	
9	2.1	AP	67	76	87	98	
		ALAT	12	54	34	23	
		Lymphocytes	2.90	2.10	2.30	2.50	
10	2.1	AP	112	345	543	323	
		ALAT	123	132	358	412	
		Lymphocytes	2.1	2.3	1.9	1.4	
11	2.3	AP	23	67	77	89	
		ALAT	34	34	67	54	
		Lymphocytes	1.80	1.90	2.10	1.20	
12	2.1	AP	123	678	NA	NA	Vomiting, anorexia, lethargy
		ALAT	134	987	NA	NA	
		Lymphocytes	1.20	0.90	NA	NA	

* Bold values are outside the normal range

AP Alkaline phosphatase (normal range 20 to 98 U/l), ALAT Alanine aminotransferase (normal range 20 to 93 U/l), Lymphocytes (normal range 1.15 to 3.4 × 10⁵ cells/μl), NA Not applicable

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