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Effect of Withdrawing Chronic Topical Immune Modulating Treatment on Schirmer Tear Test Values in Dogs with Dry Eye Disease: Relevance to Dry Eye Studies

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Abstract

Purpose: To determine the effect of discontinuing chronic topical immune modulating (IM) treatment on Schirmer tear test (STT) values in dogs with dry eye disease (DED).
Methods: Serial measurements of STTs from 14 dogs (16 eyes) previously diagnosed with DED were obtained before and after discontinuation of topical IM agents. Dogs with moderate to severe DED that had been well controlled with a topical IM treatment were included. After initial assessment topical IM treatment was discontinued, but topical lubricant was continued, and STT values were obtained sequentially. A mixed-effects regression model was used to evaluate the effects of age, gender, breed, clinical score, frequency of treatment, baseline STT value, and drug type on final STT values after IM withdrawal. $P < 0.05$ was considered statistically significant.
Results: During the follow-up period after the IM treatment had been discontinued (136 ± 29 days), 50% of the eyes ($n = 8$) exhibited STT values that never decreased to <10 mm/min. In the other 50% ($n = 8$), STT values decreased from 15.9 ± 4.7 mm/min to 6.1 ± 0.9 mm/min. In this group, the time it took to decrease the STT to <10 mm/min was 21.1 ± 9.5 days. Severe clinical signs of DED and low baseline STT pre-IM treatment significantly affected STT post-IM treatment withdrawal ($P < 0.05$).
Conclusions: The duration that a residual effect of topical IM treatment persists needs to be taken into consideration when studies are designed utilizing dogs with previous IM treatment for DED.

Keywords: cyclosporine, discontinue, immune-mediated, DED, tacrolimus, washout

Introduction

Dry eye disease (DED) is an ocular surface disease caused by tear film insufficiency/instability. DED is a relatively common canine disorder with a prevalence of ~4%.[1] A number of etiologies of DED have been reported, including neurogenic, infectious, drug-induced, congenital, and immune mediated—with immune-mediated lacrimal insufficiency being considered the most common cause in dogs.[2–5]

Most dogs with DED respond well to medical management with topical immune modulating (IM) medications such as cyclosporine A (CsA).[6] CsA is a T cell-activation inhibitor that has been widely used topically for treatment of canine immune-mediated DED for >2 decades and is currently considered to be standard of care for dogs with DED.[2,6] More recently, other types of T cell inhibitors, exemplified by tacrolimus and pimecrolimus, have also been introduced and adopted as off-label treatments of DED in dogs.[7,8]

Dogs with spontaneous DED have been well characterized and successfully utilized as an animal model of human DED in evaluating the fundamental disease mechanisms and developing novel therapeutic strategies.[2,9] The effectiveness

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of IM agents has resulted in them becoming the standard of care and are widely used by comprehensive practitioners with a concomitant decrease in the number of treatment-naive canine patients being presented to veterinary ophthalmologists.

When a study is designed to evaluate the efficacy of a new therapeutic approach to DED and utilizes dogs that have already been medically managed for this disease, it is imperative to understand the residual effect of previous treatment so as to determine a sufficient washout period. Despite its importance, there are very limited data published on the residual effect of topical IM medications in dogs with DED. The purpose of this study was to evaluate the persistence of therapeutic effect upon discontinuing topical IM treatment on Schirmer tear test (STT) I values in dogs with DED and to identify which clinical factors have significant effects on STT values obtained post-IM withdrawal.

Methods

Animals

An open-labeled prospective study including 16 eyes from 14 dogs with DED was performed. Ten dogs were client-owned dogs and 4 were purpose-bred research dogs identified with DED. Detailed information of the dogs involved can be found in Table 1. Inclusion criteria were dogs (1) with previously diagnosed DED with STT I values of ≤10 mm/min before IM therapy, (2) that had been managed with topical IM medication including CsA and/or tacrolimus, and (3) that had shown a good response to treatment resulting in an increased STT I of ≥5 mm/min from the initial (baseline) measurement, and (4) that had STT I values >10 mm/min while receiving IM treatment at the time of enrollment.

All the enrolled dogs were included in the data analysis with no drop-off. Client-owned dogs were included in this study only after obtaining permission from the UC Davis Veterinary Medical Teaching Hospital Clinical Trials Review Board and informed owner consent. All procedures adhered to Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research, and were approved by the Institutional Animal Care and Use Committee, UC Davis.

Withdrawal of treatment

The IM treatment was discontinued upon study enrollment. After IM treatment withdrawal, eyes were treated 2–4 times daily with one of following ocular lubricants, I-Drop® Vet Plus (I-MED PHARMA INC., Quebec, Canada), Optixcare (CLCMEDICA, Ontario, Canada), or Puralube VET (Dechra veterinary products, Overland Park, KS), to prevent ocular irritation and corneal damage. Eyes were closely monitored with frequent rechecks and ophthalmic examinations (every 1–4 weeks at the ophthalmologist's discretion), including STT measurement, fluorescein stain, and slit lamp examinations to monitor and document any clinical changes. No topical ophthalmic medication (including lubricant) was applied within 2 h of STT evaluation.

Ocular surface findings were scored on a 0–4 scale (0, normal conjunctiva and cornea; 1, mild conjunctival hyperemia with no corneal involvement; 2, moderate conjunctival hyperemia with mild corneal changes, including neovascularization, fibrosis, and pigmentation that affected <30% of the corneal surface; 3, moderate to severe conjunctival hyperemia with moderate corneal changes that affected 30%–50% of the corneal surface; 4, moderate to severe conjunctival hyperemia with severe corneal changes that affected >50% of the corneal surface). Scores were assigned from the images taken at each visit/examination with a digital SLR camera (Canon EOS 6D, Canon, Tokyo, Japan or Nikon D300, Nikon, Melville, NY).

The topical IM treatment was withheld until the STT I value had dropped and achieved a value of <10 mm/min or until it was determined that the STT value was unlikely to decrease to <10 mm/min. The minimum period of assessment was 40 days until this conclusion was reached. After that point, dogs resumed IM treatment or were enrolled in unrelated studies aimed at assessing a dry eye therapeutic.

Statistics

The effects of age, gender, breed, clinical score, frequency of treatment, baseline STT value and topical IM treatment type (CsA and/or tacrolimus) on final STT I values after IM treatment withdrawal were evaluated with a mixed-effects linear regression model. All the factors listed earlier were also compared (using a mixed effects logistic regression model) between the group that had a clinically significant decrease in STT values (group D: final STT <10 mm/min) and the group that did not (group ND: final STT ≥10 mm/min). In both statistic models, dogs were treated as random effects. $P < 0.05$ was considered statistically significant.

Results

Table 1 presents signalment; laterality of DED; type, duration, and frequency of previous topical IM medication; and STT values measured before and after treatment with a topical IM medication and after IM treatment withdrawal. The presumed etiology in all enrolled dogs was immune mediated, based on the therapeutic responses to IM treatment and lack of documented known risk factors or concurrent signs. The enrolled dogs were free of metabolic diseases that can cause DED, such as diabetes mellitus, hyperadrenocorticism, and hypothyroidism except 1 dog (No. 1) that had an iatrogenic hyperadrenocorticism secondary to medical treatment for concurrent immune-mediated hemolytic anemia. Although most immune-mediated DEDs are tissue-specific immune responses, concurrent systemic autoimmune disease has been reported.[3]

Of the 14 dogs enrolled, 1 had unilateral and 13 had bilateral DED. Of the latter 13 dogs, 11 dogs had only 1 eye data included in this study because the contralateral eye was disqualified for this study based on our strict inclusion criteria. Four of these dogs demonstrated insufficient responses to IM treatment (STT increased by <5 mm/min with IM treatment and/or STT after treatment did not reach 10 mm/min) in the excluded eye, whereas 7 dogs had mild disease (STT >10 mm/min and <15 mm/min with mild clinical signs).

Throughout the follow-up period after discontinuation of IM treatment, 50% of the eyes ($n = 8$, group ND) showed STT values that never decreased to <10 mm/min (136 ± 29 days, the observation period before cessation of investigation ranged from 40 to 257 days; Fig. 1A). In the other 50%

Table 1. Summary of Clinical Data on the Dogs Enrolled

Dog	*Dog type*	*Age*	*Gender*	*Breed*	*Body weight (kg)*	*Eye*	*Clinical score*	*Type of drug*	*Frequency of treatment (times/day)*	*Duration of treatment*	*Baseline STT (mm/min)*	*Post-tx. STT (mm/min)*	*Minimum postwithdrawal STT (mm/min)*	*Time to decrease STT ≤10 (mm/min) (days)*	*Follow-up (days)*
1	CO	8	M	Beagle	10.6	OD	4	T	3	174	0	12	3	9	16
2	CO	3	FS	Mixed	10.6	OS	1	CT	3	366	1	18	7	79	100
3	CO	9	FS	Mixed	9	OS	2	C	2	202	10	26	9	7	7
4	R	7	FS	Beagle	14.6	OS	3	C	2	351	7	15	7	1	20
5	R	6	FS	Beagle	12.4	OS	4	C	2	351	5	11	6	1	13
6	CO	5	FS	Pug	11.8	OD	3	C	2	159	4	17	2	28	28
7	CO	8	M	German Shepherd	25.6	OD	1	C	2	328	6	14	7	7	64
						OS	1	C	2	328	4	17	11	Never	64
8	CO	11	FS	Bichon Frise	n/a	OD	1	C	2	237	10	14	14	Never	147
						OS	4	C	2	250	5	24	8	7	147
9	CO	9	MN	Miniature Schnauzer	9	OD	2	C	2	256	4	22	17	Never	40
10	CO	2	MN	Mixed	n/a	OD	1	CT	3	117	0	13	25	Never	128
11	CO	15	FS	Toy Poodle	4.6	OD	4	T	3	54	2	19	14	Never	134
12	CO	10	MN	Mixed	5.3	OD	1	T	2	21	2	15	18	Never	90
13	R	7	FS	Beagle	16	OS	2	C	2	351	7	18	18	Never	257
14	R	6	FS	Beagle	11.2	OS	2	C	2	351	6	18	16	Never	257

CO indicates client owned dogs, R: research dogs, C: cyclosporine, T: tacrolimus, and tx.: treatment
STT, Schirmer tear test.

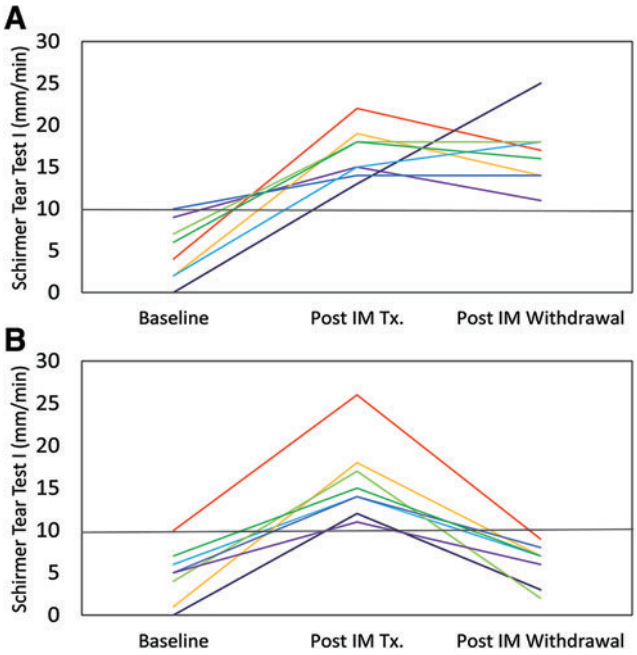

FIG. 1. **(A)** Fifty percent of the eyes ($n=8$) with KCS did not exhibit clinically significant decrease of STT I values (STT <10 mm/min) after withdrawal of topical IM treatment (CsA or tacrolimus) **(B)** whereas the remaining 50% of eyes ($n=8$) did experience a decline in STT values after withdrawal of IM treatment. *Different colors* in each graph indicate individual eye included. CsA, cyclosporine A; IM, immune modulating; STT, Schirmer tear test. Color images are available online.

($n=8$, group D), mean STT values decreased from 15.9 ± 4.7 mm/min to 6.1 ± 0.9 mm/min. In this group, the mean time it took for them to decrease to <10 mm/min was 21.1 ± 9.5 days (ranges from 1 to 79 days; Fig. 1B). In dogs in which IM therapy was discontinued in both eyes (dogs 7 and 8), 1 eye dropped to <10 mm/min and the contralateral eye did not drop <10 mm/min.

Between the groups, no significant differences in age ($P=0.36$), gender ($P=0.31$), breed ($P=0.59$), clinical score ($P=0.12$), frequency of treatment ($P=0.53$), baseline STT value ($P=0.88$), STT value at the time of IM treatment withdrawal ($P=0.64$), or drug type ($P=0.52$) was found. However, the STT values and clinical scores at baseline showed a significant positive and negative correlation, respectively, with the final post-IM withdrawal STT values ($P<0.01$). Other factors, including age, gender, breed, frequency of treatment, or drug type, failed to reveal a correlation with the post-IM withdrawal STT values ($P>0.21$).

Discussion

This study demonstrates an unpredictable effect of discontinuing topical IM treatment on STT values in dogs with DED. Upon discontinuation, there was a 50% chance of a clinically significant decrease of STT values. Statistical analyses suggest that when the STT value is low and clinical signs are severe at baseline, the patient is more likely to evidence a significant decrease in STT values after withdrawal of IM treatment.

A clinical trial in human dry eye patients has reported decreased STT and disease progression after CsA 0.05% withdrawal.[10] Although the effect of topical IM treatment on stimulating tear production in dogs is well documented,[2,7,8,11–13] there are limited and conflicting reports on the time period of residual effect after the discontinuation of medication. In a reported crossover study in normal dogs, the STT values increased from ~18 to 25 mm/min with TID treatment of 2% CsA for 7 days, and the values sharply decreased back to ~20 mm/min within 4 days of being discontinued.[2] In a case series of 20 dogs with DED successfully treated with CsA for 1 year, upon cessation of treatment recurrence of DED was noted within 2 weeks.[5]

However, another clinical study reported that 10% of dogs maintained their STT values after discontinuation of the therapy following >1 year of CsA treatment.[14] Regeneration of lacrimal gland tissue after control of chronic inflammation having been achieved with topical IM treatment has been suggested as a potential reason for the durable improvement in lacrimal function even after termination of the IM therapy.[4] Our results are consistent with the wide range of responses to IM withdrawal reported in these different studies. In our study, a large percentage of dogs did not demonstrate a marked decline in STT values during the observation period and among dogs that did have a decline, there was wide variability in the time required to document a decline and an asymmetric response between eyes of 2 individual dogs was observed.

Potential contributing factors on variable residual effect of IM treatment on STT values include variable size and body composition of dogs that may have led to different depot accumulation and clearance rate as well as different half-lives of IM treatments used and dosing frequency and duration. It is also possible that DED in some of the dogs was not immune mediated in origin, thus cessation of the IM treatment had minimal effect on STT values.

Limitations of the study reported here include the relatively small number of dogs evaluated and the reliance of response to IM therapy as the sole indicator that the underlying cause of the initial low STT values was attributable to insidious immune-mediated dysfunction of lacrimal tissues. That being said, the assessment we performed on the dogs enrolled is standard for determining eligibility for entry into a dry eye treatment trial. Use of different types of IM therapy and ocular lubricants among dogs before enrollment in this study is another limitation due to the nature of the veterinary patient-based study. Other limitations include the variety of age, breed, and gender of the dogs, and the wide range of time from the onset of disease to diagnosis, treatment, and enrollment in the study.

In drug development studies using dogs with spontaneous DED, the effectiveness of a given therapeutic is often compared with the effect of CsA. Our results suggest that firm entry criteria need to be established for studies evaluating the lacrimo-stimulating effects of therapeutics in dogs with DED. Caution should be used when interpreting studies that do not provide a defined washout period upon cessation of IM treatment coupled with documentation of a drop in STT values. Further study is needed to define the risk factors for STT decrease after cessation of topical IM treatment, which could subsequently be applied to the clinical setting.

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Author Disclosure Statement

No competing financial interests exist.

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