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LACRIMOMIMETIC EFFECT OF TOPICAL CYCLOSPORINE A IN CANINE KERATOCONJUNCTIVITIS

EFEITO LACRIMOMIMÉTICO DA CICLOSPORINA A TÓPICA EM CERATOCONJUNTIVITE SECA CANINA

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SUMMARY

The authors make a description of the results attained with the topical use of keratoconjunctivitis sicca. In all treated cases they observed an increase in the values of the Schirmer tear test marked improvement of the eyes and furthermore an attenuation of the melanic pigment deposited on the cornea.

UNITERMS: Keratoconjunctivitis sicca; Cyclosporine; Dogs

INTRODUCTION

Canine KCS is a relatively frequent sickness and its therapeutic approach presents some difficulties, essentially for two reasons. These reasons are the impossibility in most cases of regaining an optimal lacrimal function and the problems which the dog's owner must endure in order to efficiently substitute the lack of lacrimal fluid during the dog's life.

The sickness will lead, in time, to blindness, due to corneal melanic pigment deposits and, in more severe cases, keratinization. In most cases, it will get to this point after having gone through a more or less long period of ocular irritation which is very troublesom for the patient and owner. This situation is aggravated by the fact that, with a very high frequency, this pathology is mistaken with a non-specific conjunctivitis and treated, thus leading to therapeutic failure and to the owner's dismay.

Recent evidences lead to the probable existence of an immunological etiology in most cases of dry eye^{1,4,5,6,7}. This would point out to the convenience of employing immunosuppressive agents, such as cyclosporine A, as a therapeutic mean.

This would be done having in mind the possibility of arresting the immunological process, restoring the functionality of the lacrimal glands, healing the corneconjunctival lesions and installing a less intensive therapy (less frequent medication), which will imply a lesser burden for the dog's owner.

Accordingly to the above mentioned, we started this therapeutic trial, in order to evaluate the use of cyclosporine A in oily solution, in dogs with KCS. The objective of this work is to show the results obtained in the treatment of 15 clinical cases of KCS.

MATERIAL AND METHOD

Fifteen dogs were chosen. Its description can be seen in Tab. 1. The inclusion criterion in the present protocol was the previous existence of a chronic corneconjunctival process, with an evolution period ranging between 1 and 15 months, registered through anamnesis and by ophthalmological interview.

Most of the cases had presented during that period, as described by the dog's owner, different degrees and types of secretion (mucous to purulent). Prescribed medications had been generally non-specific, such as antibiotics, ocular cicatrizants and antiinflammatories. Until these animals were included in the present study, none of them had a diagnosis of KCS and, therefore, had been devoid of specific treatment.

KCS was diagnosed based on the presence of characteristic clinical signs and the evaluation of lacrimal production through the Schirmer's Test. The following scale was used =

> 10 mm/minute : NORMAL
5 to 10 mm/minute : SUSPICIOUS
< 5 mm/minute : POSITIVE FOR KCS

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TABLE 1

Summary of all patients included in the study and Schirmer's Test values for both eyes in first and following interviews (days 14 y 30). Buenos Aires, 1991.

Nº	Breed	Sex	Age (Y)	Schirmer Tear Test (mm/min)					
				1 st Interview		Day 14		Day 30	
				R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
1	Pekings	F	10	2	4	6	10	9	12
2	Cocker Amer	M	3	3	4	7	12	13	15
3	Pirineos Sheepdog	F	5	1	3	3	9	7	10
4	Mongrel	M	6	0	2	10	9	15	11
5	Mongrel	F	14	0	0	2	3	3	2
6	Cocker Amer	M	8	0	4	7	6	13	7
7	Cocker Amer.	M	10	2	3	7	5	12	11
8	Cocker Amer	F	4	0	0	3	5	*	-
9	Cocker Amer	F	7	0	2	5	9	*	*
10	Cocker Amer	F	5	1	2	12	11	15	13
11	Mongrel	M	7	0	11	7	13	9	15
12	Utsa Apsu	M	8	3	7	4	7	10	12
13	Utsa Apsu	M	6	5	4	8	9	10	14
14	Pekinges	M	9	0	0	3	2	5	4
15	English Cocker	M	7	4	6	9	10	7	14

F = Female
M = Male
R.E = Right eye
L.E = Left eye
Y = year
* = not examined

It was also taken into account, the degree of corneal vascularization, the amount of mucous secretion and the intensity of pigmentation at the moment of interview. All 15 dogs were treated during the beginning period exclusively with a 2% oily Cyclosporine A solution, one drop 3 times daily. As control days, we established days 14 and 30 after the first interview. Routine ophthalmologic examination and Schirmer Tear Test were done on each clinical consultation.

Schirmer's Tear Test values for both eyes for first and following days (14 and 30) were recorded as basic information in this first experience.

RESULTS

From the original 15 patientes included in this study, we were able to complete the follow up on day 30 in only 13, having lost contact with cases 8 and 9.

At the beginning of the experience, 11 patients (73.33%) showed bilateral KCS, with mean secretion values, measured by Schirmer's Tear Test of 1.36 mm/min. for the right eye (ranging between 0 and 4 mm/min.). The other 4 patients showed positive values for unilateral KCS of the right eye,

with an average value of 2.5 mm/min. In three of these cases, the contralateral eye showed suspicious values (mean of 5.5 mm/min. in cases 7, 12 and 15). The last of the 4 cases had normal value for the contralateral eye (11 mm/min.). Follow up of the KCS cases is shown in Tab. 2.

TABLE 2

Change in lacrimal secretion measured with Schirmer's Tear Test in KCS unilateral cases treated with cyclosporine A (4 cases). Buenos Aires, 1991.

E Y E	FIRST INTERVIEW			CONTROL DAY 14			CONTROL DAY 30		
	+	S	N	+	S	N	+	S	N
R	4	-	-	1	3	-	-	3	1
L	-	3	1	-	1	3	-	-	4

R = Right
L = Left
+ = Positive value for KCS
S = Suspicious value for KCS
N = Normal values of lacrimal secretion

The data analyzed on day 14 displayed a significant variation in the values of the Schirmer's Tear Test which allowed for a recategorization of the patients within the scale of test.

In this opportunity, the 11 cases of bilateral KCS showed an average increase of lacrimal secretion of 268.32% for both eyes. This means an initial average value of 1.816 mm/min. for both eyes vs. a value of 6.86 mm/min. on day 14, with a net increase in lacrimal production of 5.044 mm/min. For the right eyes, the initial average value of 1.36 mm/min. went up to 6 mm/min. (net increase of 4.64 mm/min.), which would result in an 341.18% increase. For the left eye, average values went up from 2.27 mm/min. to 6.73 mm/min., with a net increase of 4.46 mm/min. (196.48%). Results are shown in Tab. 3.

TABLE 3

Change in lacrimal secretion measured with Schirmer's Tear Test in 9 cases of bilateral KCS treated with cyclosporine A. Buenos Aires, 1991.

E Y E	First Interview			Control Day 14						Control Day 30					
	+	S	No	+		S		No		+		S		No	
				N	%	N	%	N	%	N	%	N	%	N	%
R	9	-	-	3	33	4	44	2	22	1	11	3	33	5	55
L	9	-	-	2	22	4	44	3	33	2	22	1	11	6	66

R = Right
L = Left
+ = Positive value for KCS
S = Suspicious value for KCS
No = Normal values of lacrimal secretion
N = Number of cases

One day 30, there was a marked increase in the trend shown in day 14 (Fig. 1). Over 9 cases, average values for the right eyes were 10 mm/min., with a net increase of 8.64 mm/min. (635.29% increase in relation to the initial value). For the left eyes, average value was 9.79 mm/min., with a net increase of 7.51 mm/min. (330.84%).

The mean overall increase in global lacrimal secretion was 483.07% (Tab. 4).

TABLE 4

Change in Schirmer's Tear Test values after 30 days of topical treatment with cyclosporine A in 9 patients with bilateral KCS. Buenos Aires, 1991.

EYES	FIRST INTERVIEW MM/MIN.	CONTROL DAY 14 MM/MIN. *	CONTROL DAY 30 MM/MIN. *
RIGHT	1.23	4.64 (341.18%)	8.64 (635.29%)
LEFT	2.27	4.46 (196.48%)	7.51 (330.84%)

* Values given as net increase in lacrimal secretion

Of the group of patients under study, only 2 of them (13.33%) were found with abnormal results to the Schirmer's Tear Test at the end of the experience to attain an average increase in lacrimal secretion of 3.5 mm/min. It is interesting to note that, at the beginning of treatment, these two patients showed zero results to the Schirmer's Tear Test in both eyes. All of the other 13 patients (86.67%) reached normal average values for both eyes (10.64 mm/min. for the right eye and 12.45 mm/min. for the left one) (Fig. 2).

This favorable evolution of the lacrimal secretion was accompanied by an improvement of the clinical appearance of the eyes (Fig. 1, 2, 3 and 4). The typical mucous secretion of this sickness was notably reduced at the first control and completely disappeared by the time of the final control day. Also, the corneal vascularization showed by some of the patients at the first interview was reduced or disappeared, in correlation with the increase in lacrimal secretion. In some cases it was possible to observe a decrease in corneal pigmentation.

DISCUSSION

KCS is a sickness that presents two relevant treatment problems: one is lack of knowledge of its etiology and the other is high incidence of diagnostic error.

As to the etiology, bibliographical references of the last 3 years suggest that a high percentage of KCS in dogs is triggered by an immunological reaction.

Recent research on experimental models show in lacrimal glands a change in the relationship between T suppressor and T helper cells, with an increase of T helpers^{3,5}.

Cyclosporine A is a non cytotoxic immunosuppressor drug, used to reduce rejection in organ transplants⁴. Its main effect is inhibition of T helper cells, favoring thus the action of T suppressor cells. This effects leads the balance of the immunological regulation carried on by T cells, towards immunotolerance^{2,3,4,6}.

The use of cyclosporine A as a means to revert glandular adenitis was considered on the basis of results from experimental models and based on the hypothesis that canine KCS is produced by a deficiency in T suppressor cells activity⁷.

CONCLUSIONS (see Fig. 3, 4, 5 and 6)

1. Every treated case showed an increase in lacrimal secretion, ranging from a minimum value of 3.5 mm/min. to a maximum of 12.45 mm/min.;
2. 86.67% of the patientes (13 out of 15) recovered normal values of lacrimal secretion;
3. Marked reduction, and in some cases, complete disappearance of the mucous secretion typical of this sickness, were observed at the time of the first control (day 14);
4. Most of the treated eyes recovered their normal aspect and it was possible to observe partial or total remission of conjunctival vascularization and hyperemia;
5. Pigment mobilization was observed in some cases, with an improvement of the corneal transparency.

RESUMO

Realizou descrição dos resultados obtidos com o uso tópico da Ciclosporina A em casos clínicos de ceratoconjuntivite seca em cães. Observam que em todos os casos tratados houve o aumento dos valores da prova de Schirmer, melhora marcada do estado clínico dos olhos e depositado sobre a córnea.

UNITERMOS: Ceratoconjuntivite seca; Ciclosporinas; Cães

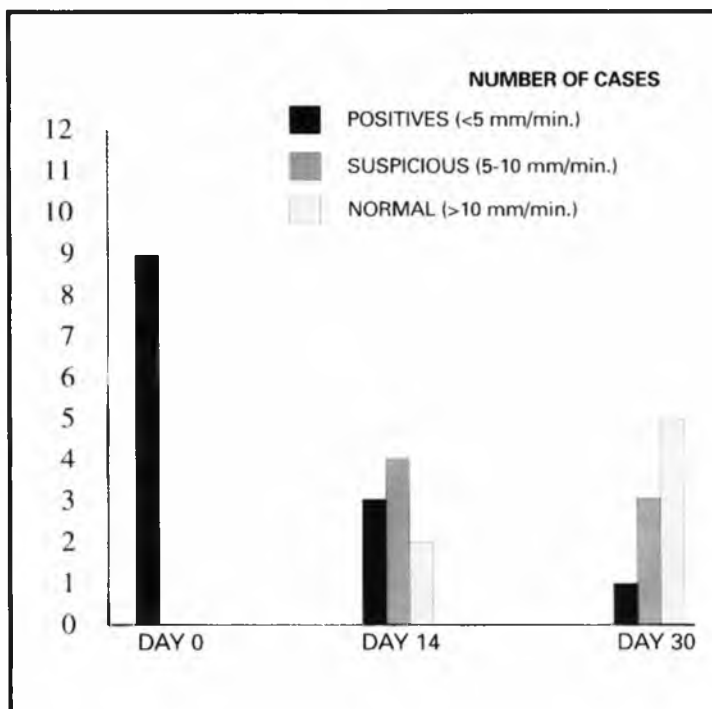


FIGURE 1
Improve of cases on day 14 and day 30 controls.

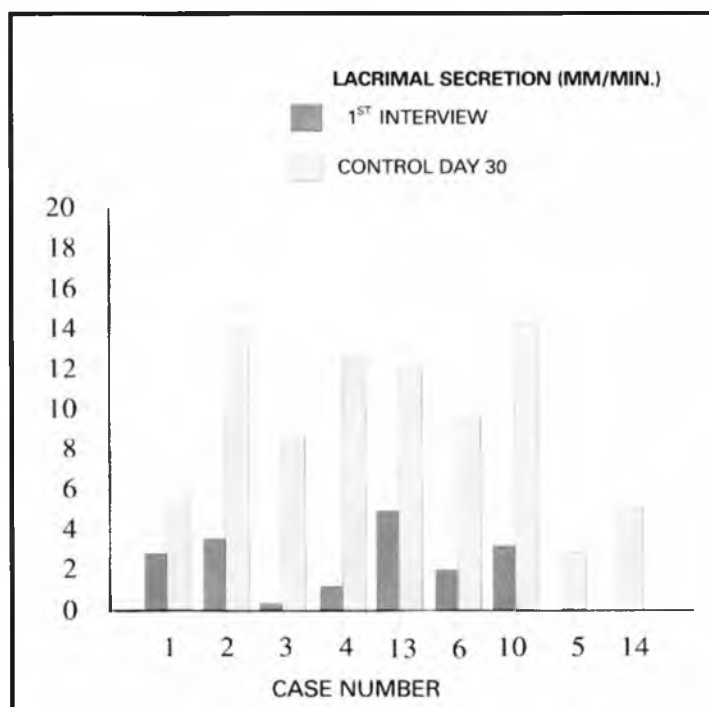
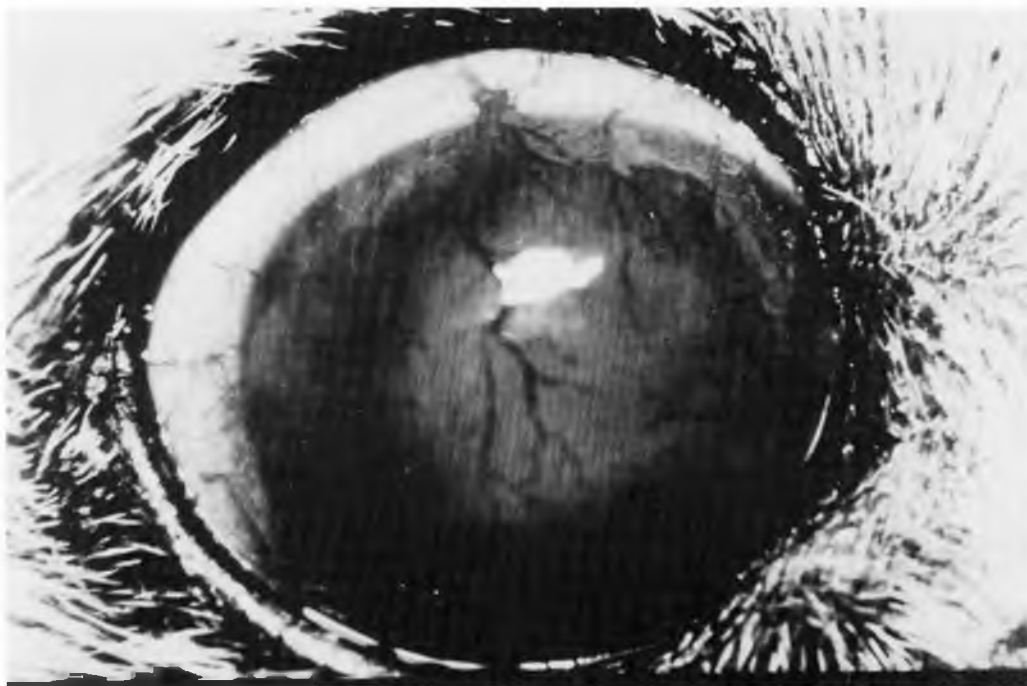


FIGURE 2
Values on lacrimal secretion on 1st interview and day 30 control before topical treatment with cyclosporine A.



A



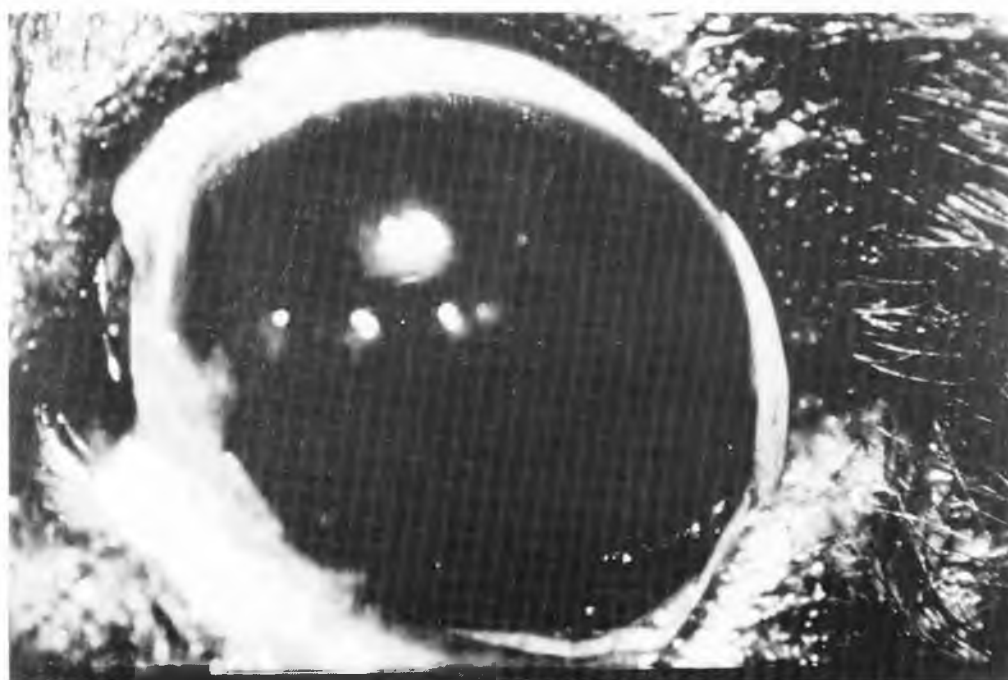
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FIGURE 3

Case nº 11 - A - Day 0, STT 0 mm/min.
B - Day 14, STT 7 mm/min.



A

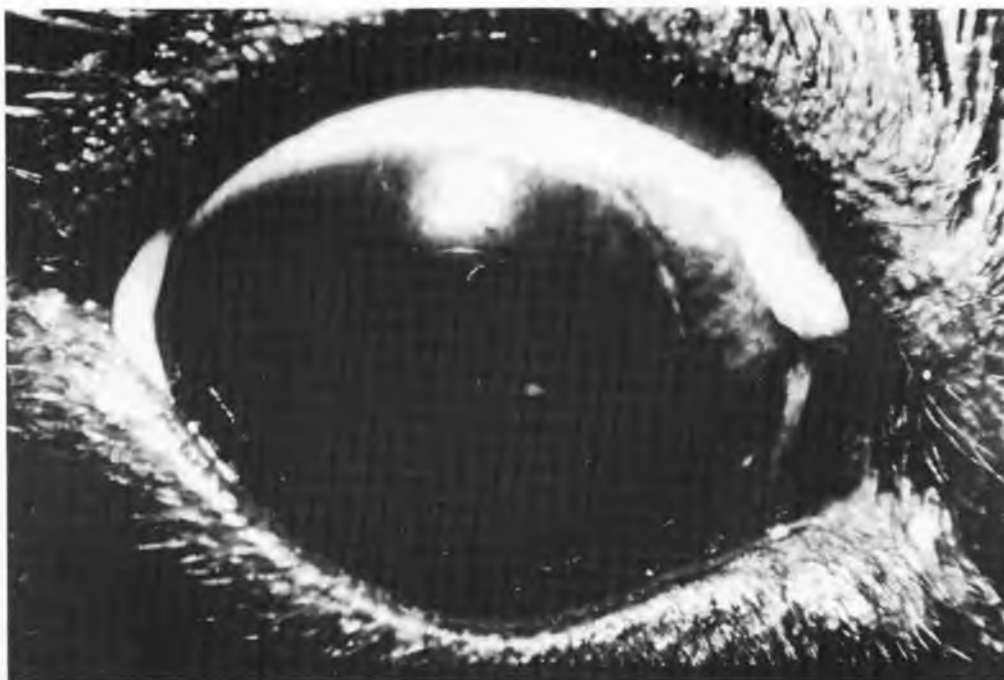


B

FIGURE 4

Case nº 10 - A - Right eye: Day 0. STT 4 mm/min.

B - Left eye: Day 0. STT 2 mm/min.



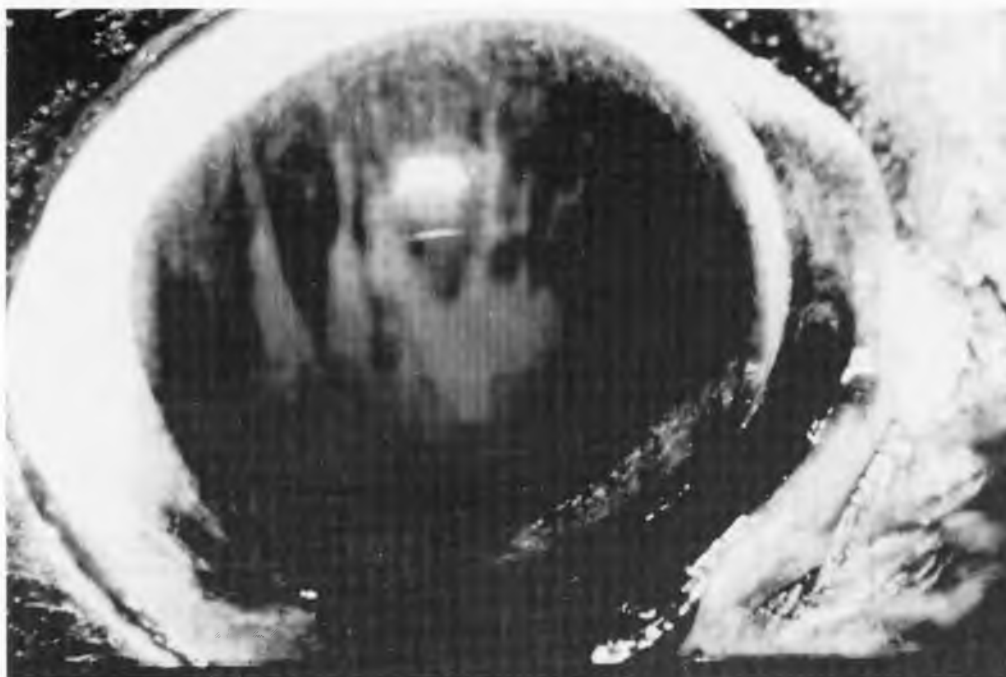
A



B

FIGURE 5

Case n^o 10 - A - Right eye; Day 14, STT 12 mm/min.
B - Left eye; Day 14, STT 11 mm/min.



A



B

FIGURE 6

Case nº 10 - A - Right eye; Day 50. See the pigment mobilization and corneal transparency.
B - Left eye; Day 50.

REFERENCES

- 01-BACHRACH, A.; SCAGLIOTTI, R. Topical cyclosporine for KCS. **Advanc. SAM.**, v.1, p.1-2, 1988.
- 02-BEN EZRA, D.; PETER, J.; BRODSKY, M.; COHEN, E. Cyclosporine eye-drops for the treatment of severe vernal keratoconjunctivitis. **Amer. J. Ophthalm.**, v.101, p.278-82, 1986.
- 03-BLOEMENA, E.; VAN OERS, M.H.J.; WIENREICH, S.; YONG, S.L.; SCHELLEKENS, P.A. Prednisolone and ciclosporin A exert differential inhibitory effects on T-cell proliferation *in vitro*. **Clin. Immunol. Immunopathol.**, v.48, p.380-91, 1988.
- 04-KASWAN, R.L. Intraocular penetration of topically applied cyclosporine. **Transplant. Proc.**, v.20, p.650-5, 1988.
- 05-KASWAN, R.L.; FISCHER, C.A.; WARD, D.A.; MARTIN, C.; RAMSEY, J. Clinical trials of ophthalmic cyclosporine in chronic keratitis. **Trans. Amer. Coll. Vet. Ophthalm.**, v.18, p.276-95, 1987.
- 06-KASWAN, R.L.; SALISBURY, M.A.; WARD, D.A. Spontaneous canine keratoconjunctivitis sicca, a useful model for human KCS: treatment with cyclosporine eyedrops. **Arch. Ophthalm.**, v.107, p.1210-6, 1989.
- 07-KERN, T. Topical cyclosporine therapy for keratoconjunctivitis sicca in dogs. **Cornell. Vet.**, v.79, p.207-9, 1989.

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