Successful treatment of keratoconjunctivitis sicca (KCS) in dogs with pimecrolimus eye drops: a comparison with cyclosporin A (CyA) ophthalmic ointment

Program # 69

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Purpose

KCS is a progressive inflammation of the cornea and conjunctiva resulting from deficient tear production. The disease afflicts millions of patients worldwide, and its symptoms are reported by 17-25% of patients in ophthalmic clinics (1). The disease is also prevalent in dogs, accounting for 1.5% of all canine cases in Veterinary Teaching Hospitals in the USA (2). Indeed, the dog is an accepted naturally-occurring animal model of the disease, and topical cyclosporin A (CyA), which has recently been approved for treatment of KCS in humans, has been the treatment of choice by veterinarians for 15 years (3). Pimecrolimus has proven to be superior to CyA in animal models of skin inflammation after both topical and systemic administration (4). In previous pilot trials, pimecrolimus has shown significant activity in animal models of immune-mediated inflammatory eye diseases (see same session poster # 131). The aim of this study was to conduct a clinical trial, testing the efficacy of topical pimecrolimus in alleviating clinical signs of KCS in dogs and compare it with a veterinary commercial form of CyA (Optimmune®).

Methods

Study design: An open-label, multicenter, randomized, 8-week outpatient clinical dog study was conducted in Germany, Spain and Switzerland. All dog owners read an information sheet and signed an informed consent prior to participation.

Inclusion criteria: Dogs of either gender and of any breed or age were enrolled in the study provided that

1) uni- or bilateral KCS was diagnosed based on medical history, a Schirmer tear test (STT) value ≤ 10 mm/min. and a total score ≥ 4 in grading clinical signs of conjunctival and/or corneal inflammation (the following 9 signs were evaluated and scored from 0=none to 4=severe: blepharospasm, conjunctival thickening, conjunctival hyperemia, conjunctival pigmentation, corneal pigmentation, corneal edema, corneal vascularization, corneal infiltration and amount of ocular discharge)

2) the animals have not been previously treated with topical or systemic CyA.

Before being included in the trial, the dogs had to meet additional stringent criteria related to other previous treatments and surgeries, and to associated systemic or ocular diseases.

Study protocol: Dogs were randomly assigned to a treatment group, to be medicated twice daily for 8 weeks in both eyes with 1% pimecrolimus experimental oil-based eye drops or 0.2% CyA ophthalmic ointment (Optimmune®). Upon enrollment and at weeks 2, 4 and 8, all dogs underwent complete physical and ophthalmic examinations, including slit-lamp biomicroscopy, STT and indirect ophthalmoscopy.

Statistical methods: Between-treatment differences in change from baseline in STT value and in the total ocular sign score were analyzed by ANOVA and the Wilcoxon rank sum test, respectively. Responder analysis was made by Fisher's exact test. As there were no substantive differences between the worst-eye and best-eye analyses, the results for only the worst-eye (with the lowest STT value at baseline) are summarized.

Results

Study population

Of the 47 dogs that were randomized into the study, 44 dogs completed the study. The total number of eyes evaluated was 77, of which 40 eyes (24 dogs) were treated with CyA and 37 eyes (20 dogs) were treated with pimecrolimus. Terriers (n=12) were the largest group of dogs enrolled, followed by Spaniels (n=9) and Shi Tzus (n=7). The demographic characteristics of the study population are listed in Table 1.

Table 1: dog demographics

	ASM981 1%	CyA 0.2%	Total	P value*	
Gender					
Female	10 (50%)	14 (58%)	24 (55%)	0.762	A
Male	10 (50%)	10 (42%)	20 (45%)		
Neutered					
Yes	5 (25%)	4 (17%)	9 (21%)	0.711	A
No	15 (75%)	19 (79%)	34 (77%)		
Unknowm	0 (0%)	1 (4%)	1 (2%)		
Age (years)					
Mean	7.5	6.9	7.2	0.547	B
S.D.	3.0	3.3	3.2		

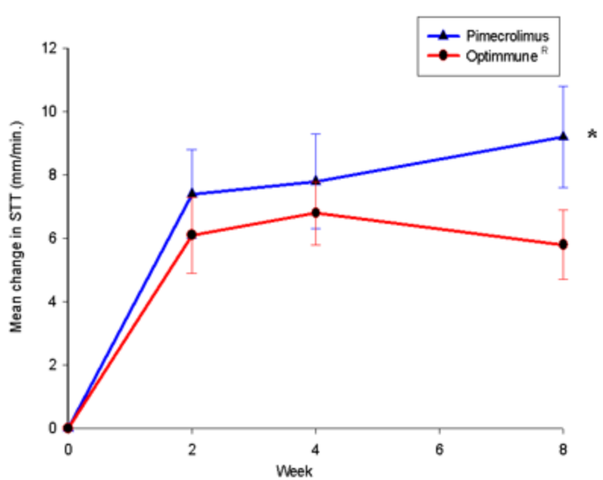
*Results from statistical tests of treatment group comparability
A: Fischer's exact test. B: Wilcoxon rank sum test

Changes in tear production

At baseline, the mean STT values in the pimecrolimus and the CyA groups were 3.8 ± 0.7 mm/min. (n=20) and 4.6 ± 0.7 mm/min. (n=24), respectively. Statistically significant improvements from baseline were observed within both groups (P ≤ 0.001) at all follow-up visits (Fig.1). After 8 weeks of treatment, mean increases of 9.2 and 5.8 mm/min. were seen in the pimecrolimus and CyA groups, respectively. At this time, although the difference was marginally significant (P=0.085; by-visit ANOVA), pimecrolimus tended to be more effective than CyA by 3 to 3.5 mm/min.

Dogs responding to treatment were defined as those in which STT values increased to more than 10 mm/min. About 60% and 50% of dogs responded to pimecrolimus and CyA, respectively (P=0.36).

Figure 1: Mean change (± sem) from baseline in STT values over time



*** Marginally significant difference compared to CyA (P=0.085; by-visit ANOVA)**

Effect on clinical signs of inflammation

At baseline, the mean total scores for signs of corneal and conjunctival inflammation (9 signs evaluated; maximum total score = 36) in the pimecrolimus and the CyA groups were 16.0 ± 1.1 (n=20) and 13.9 ± 1.4 (n=24), respectively (Table 2). Statistically significant improvements from baseline were observed within both groups (P ≤ 0.001) at all follow-up visits. After 8 weeks of treatment, there was a significantly larger reduction in the total score in eyes treated with pimecrolimus (mean decrease of 10.3) as compared to eyes treated with CyA (mean decrease of 7.6; P=0.024). Significant differences in favor of pimecrolimus were noted in conjunctival thickening (P<0.001), and marginally significant differences in blepharospasm at week 2 (P=0.078), in conjunctival hyperemia at weeks 4 (P=0.088) and 8 (P=0.078) and in corneal infiltrates at week 8 (P=0.093).

Table 2: Mean change (± sem) from baseline in total score over time

Treatment Group	N	Baseline	Mean change from baseline		
			Week 2	Week 4	Week 8
Pimecrolimus	20	16.0 ± 1.1	- 5.0 ± 0.4	- 7.9 ± 0.6	- 10.3 ± 0.8 *
CyA	24	13.9 ± 1.4	- 4.7 ± 0.8	- 6.5 ± 1.0	- 7.6 ± 1.2

N: number of dogs; * P ≤ 0.05 compared to CyA (Wilcoxon rank sum test)

Subgroups of dogs were examined on the basis of the initial KCS severity [severe KCS: STT = 0-2 mm/min.; moderate KCS: STT = 3-6 mm/min.; mild KCS: STT ≥ 7 mm/min.]. Important improvements, were observed in all subgroups after administration of pimecrolimus or CyA.

Side effects

Two dogs assigned to the pimecrolimus group were discontinued a few days after enrollment because of adverse events, mostly intense pain. Transient irritation following treatment was noted in 6 dogs treated with CyA and in 3 dogs treated with pimecrolimus. Two dogs (one in each group) experienced „excessive lacrimation" attributed to the treatment. Corneal lipidosis was noted in one CyA-treated eye.

References

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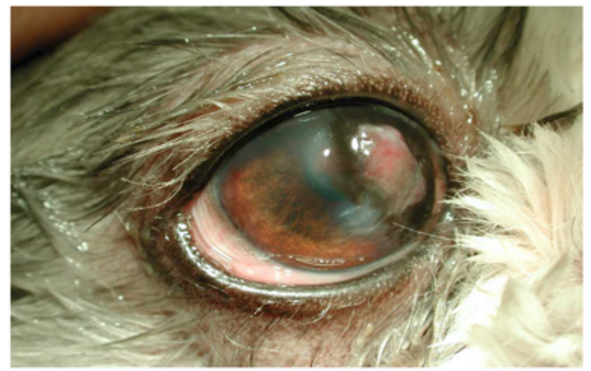
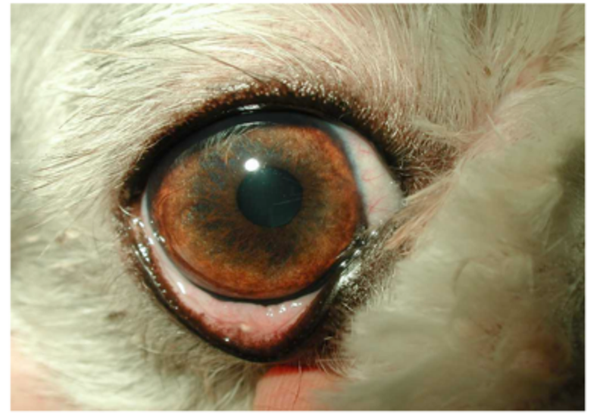
4. Meingassner JG, Grassberger M, Fahrngruber H et al (2001) A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. Brit J Derm;144:788-94.

Right eye of patient 111, a 4.5 year old male Shi Tzu

Top: At presentation. STT = 3, clinical score = 20.
Bottom: After 8 weeks of treatment with pimecrolimus. STT= 9, clinical score = 8.





Conclusion

Both treatments caused a significant increase in tear production, and a significant improvement in signs of inflammation, within 2 weeks. Tear production remained high in both groups throughout the experimental period, and continued improvement in clinical signs was noted for the duration of the study.

Although the difference was marginally significant, pimecrolimus tended to be more effective than CyA in increasing tear secretion after 8 weeks of treatment. Moreover, pimecrolimus was statistically superior to CyA in reducing the total score for signs of corneal and conjunctival inflammation.

The results of this study show that 1% pimecrolimus oily eye drops are more effective than the commercial 0.2% CyA ophthalmic ointment in controlling KCS in dogs. These findings confirm the interest to develop pimecrolimus as a therapy for dry eye.

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