Ocular distribution of Tacrolimus after topical administration as EyeSol formulations in rabbits and dogs

Sonja Krösser, PhD[1] , Johannes Korward, MSc[1], John D. Sheppard, MD[2], Victor L. Perez, MD[3]

[1] Novaliq GmbH, Heidelberg, Germany, [2] Old Dominion University, Norfolk, VA, United States, [3] University of Miami, Miami, FL, United States

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Introduction

Tacrolimus is a highly potent calcineurin inhibitor, mainly used as systemic immunosuppressant. One application of tacrolimus, albeit off-label, is the oral administration for the treatment of uveitis. EyeSol® is a water-free technology platform with excellent spreading properties and long residual time on the ocular surface. It therefore has the potential to deliver tacrolimus to the uvea after topical administration. The use of eye drops could lead to a safe and convenient alternative to the current use of high dose steroids or orally administered calcineurin inhibitors, both of which carry risks for significant side effects.

To investigate the ocular distribution after topical ocular administration, the pharmacokinetics of different tacrolimus EyeSol® formulations was studied in rabbits and dogs.

Methods

New Zealand White (NZW) rabbits and Beagle dogs received multiple topical ocular doses of tacrolimus (as 0.03% solution [dog and rabbit] or 0.03%, 0.1%, 0.3% suspension [rabbit only]): one drop in both eyes three times daily for 3 days and a single dose on Day 4. Animals were then sacrificed at specific timepoints after the last dose (rabbit: 0.5h, 1h, 2h, 4h, 8h, 24h; dog: 1h, 4h). Ocular examinations were conducted to observe potential irritation related to the test article.

		Tacrolimus formulations			
		0.03% solution	0.03% suspension	0.1% suspension	0.3% suspension
		Tacrolimus tissue concentration [ng/g]			
Cornea	C_{max}	3130	511	968	1920
	AUC	16600	8070	12000	19900
Conjunctiva	C_{max}	287	568	865	6620
	AUC	2445	2500	5610	25950
Iris/Ciliary Body	C_{max}	113	21.3	49.3	88.1
	AUC	1280	326	744	1330
Sclera	C_{max}	119	365	185	1110
	AUC	1450	1480	2610	5660
Choroid/RPE	C_{max}	14	7.04	20.2	60.8
	AUC	228	87.7	232	413
Retina	C_{max}	10.6	4.12	8.67	27.9
	AUC	226	68.3	170	380

Table 1: Comparison of PK parameters in ocular tissues after repeated topical ocular administration of different tacrolimus formulations to rabbits

Ocular tissues were collected, and levels of tacrolimus were determined in aqueous humor, cornea, vitreous, bulbar and palpebral conjunctivae, iris/ciliary body, retina, RPE/choroid, sclera and blood using an adequately qualified LC-MS/MS method.

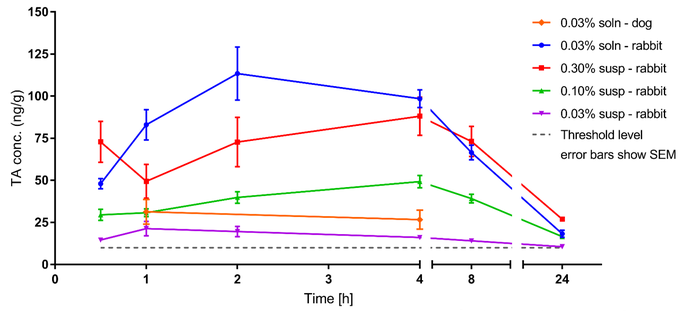

Figure 1: Concentrations of tacrolimus in iris/ciliary body after topical administration of EyeSol solutions or suspensions to rabbits or dogs

Results

In both species, the highest mean concentrations of tacrolimus were observed between 0.5 and 2 hours post dose in the anterior segment of the eye, as expected for a topical treatment. Significant concentrations reached the uvea at levels well above the recommended serum level that was found to be predictive of disease control in uveitis after systemic administration (10 ng/g) (Figure 1).[1] For the highest dose levels tested (0.03% solution and 0.3% suspension) pharmacologically relevant retina exposure was also detected in rabbit (Table 1; Figure 3).

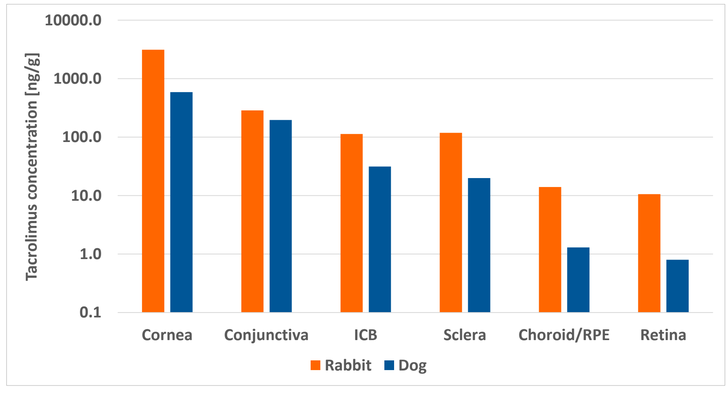

Figure 2: Species comparison of tacrolimus maximum tissue concentrations (ng/g) after topical administration of 0.03% tacrolimus solution in EyeSol to rabbit and dog

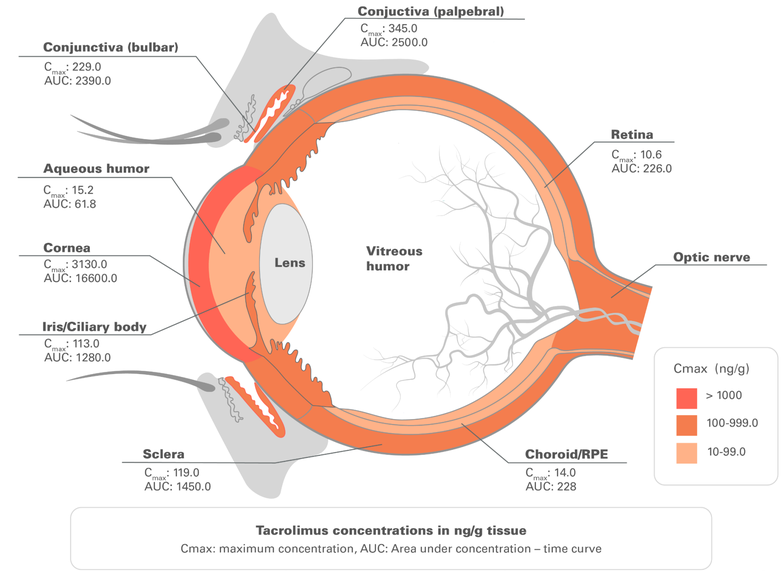

Figure 3: PK parameters for ocular tissues after repeated dosing of 0.03% tacrolimus solution in EyeSol to rabbits

Systemic concentrations were below or around the LLOQ of the method (0.05 ng/mL) and therefore regarded negligible, and all formulations were well tolerated in both studies. The comparison of different formulations in the rabbit study showed a dose response for all three suspensions, and the 0.03% solution was comparable to the highest suspension dose (Table 1). The tissue concentrations in rabbits were approx. 3 times higher compared to dogs in most tissues, which is not unexpected considering species differences, e.g. presence of nictitating membrane in rabbits, large size of dog eye combined with higher corneal thickness. The distribution pattern of all test articles was overall comparable across species (Figure 2).

Conclusions

- Repeated topical ocular dosing of tacrolimus in EyeSol® resulted in pharmacologically active levels of tacrolimus in the uveal target tissues, in both rabbit and dog
- Species specific differences in anatomy led to different but still sufficient and relevant tissue levels in dogs compared to rabbits

These results together with published findings from *in vivo* models indicate the potential for a tacrolimus formulation as a novel topical treatment option for uveitis.[2]

References: 1) Luis et al. Ocul Immunol Inflamm (2022) 1654-1658; 2) Majumdar et al. Curr Molelcular Medicine 17 (2017) 1-10

Disclosures: **J. Sheppard and V. Perez (consultants to Novaliq); S. Krösser and J. Korward (employees of Novaliq)**

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