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Cyclosporine A (CsA) concentrations in aqueous and vitreous humour samples and clinical and ophthalmological findings in 16 equine eyes after implantation of a sustained-release CsA delivery device

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Summary: Suprachoroidal and subconjunctival implantation of devices which provide a sustained release of cyclosporine A (CsA) have been repeatedly described to have a beneficial effect on eyes suffering from ERU or immune-mediated keratitis. These implants are thought to deliver CsA into the eye and eye-tissues for a period of about three years. However, some horses which have been treated with a CsA implant show an ongoing inflammation and a deterioration of the ocular findings within months after having received the device. Several horses which have been treated previously with implantation of a CsA pellet have been submitted to the Equine Clinic of the Ludwig-Maximilians-University of Munich. Only one eye in each horse had been subjected to CsA pellet implantation. One horse had received three implants in one instance, another horse had received two implants within 4 months. Two implants were located suprachoroidally and 14 implants were located subconjunctivally or episclerally. Intraocular samples could be taken from 16 of those horses. Ten of these horses suffered from recurrent uveitis and underwent vitrectomy, which provided undiluted vitreous humour that could be taken at the beginning of surgery. One of these horses had been rubbing the eye since the implantation of the device. Three horses had a chronic keratitis and two horses had a chronic iritis. Aqueous chamber fluid was taken from these five horses for laboratory tests regarding an intraocular leptospiral infection and all were tested negative. The last eye had suffered from a chronic kerato-uveitis of unknown cause for a long time, and had developed a severe atrophy requiring enucleation. After removal, a vitreous humour sample could be taken. The sampling of intraocular fluids was performed 3 months up to 3 years after the implantation of the CsA devices. All intraocular fluid samples were tested for cyclosporine concentrations. The lowest detection limit was 10 µg/l. No CsA could not be detected at all (CsA < 10 µg/l) in all but one of the intraocular samples. The only sample in which CsA was detected (38.5 µg/l), had received three CsA implants 4 months previously. The CsA implants were removed in 8/10 horses in which a vitrectomy was performed because they provided no benefit and lay in positions disturbing the laser-sclerotomy required for vitreous surgery. All but one implant were located episclerally. No further bouts of uveitis occurred after vitrectomy. The CsA implants had to be removed in the horses suffering from keratitis to allow corneal healing by vascularisation. One of these implants was located suprachoroidally. It can be concluded that CsA cannot be detected in intraocular fluid samples when just one CsA device is used, not even during the first six months after implantation, independent of its location. However, a very low and indetectable concentration of CsA may be present which reduces uveitis activity. A low concentration of CsA could be detected (38.5 µg/l) in the horse with three CsA devices which had been placed episclerally. In the case of eyes suffering from chronic keratitis, vascularisation of the cornea may have more benefit than immunosuppressive medications including CsA devices.

Keywords: cyclosporine A, sustained delivery, concentration, intraocular fluid samples, equine recurrent uveitis, ERU, Keratitis

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Introduction

About a decade after establishing vitrectomies in horses suffering from equine recurrent uveitis (ERU) (*Werry* and *Gerhards* 1991, 1992), different kinds of CsA implants providing sustained drug release have been described by veterinary ophthalmologists from the United States as another treatment option of ERU (*Gilger* et al. 1998, *Gilger* et al. 2000, *Gilger* et al. 2001). Silicone-coated cyclosporine pellets and cyclosporine in a polyvinyl alcohol polymer (bioerodible implants) have been described (*Gilger* and *Michau* 2004, *Kim* et al. 2005, *Gilger* et al. 2006, *Lee* et al. 2007, *Gilger* et al. 2010) (see Table 1). They were used in horses suffering from ERU with the intention of stopping or at least reducing uveitis recurrences and preserving vision and were described to be well-tolerated. It was assumed that ERU was an autoimmune disease and was unrelated to any infectious agents. Consequently, CsA was considered an ideal drug for the treatment of recurrent uveitis. The first surgeries were performed by implanting the CsA device into the vitreous cavity. Later on, matrix-reservoir biodegradable CsA pellets were implated deep into the sklera or suprachoroidally instead of intravitreally because of subsequent complications. Subcon-

junctival or episcleral implantation did not lead to measurable concentration of CsA inside the globe and, therefore, was not an option for the treatment of ERU (*Gilger* et al. 2006).

The average number of inflammatory bouts of ERU had been 7.5/year prior to the CsA implantations and, respectively, 0.36/year after the implantations (*Gilger* et al. 2006). A multicentre follow-up study after an average of 2.5 years after implantation of suprachoroidal CsA devices was performed in 151 eyes in 2010. The result was that vision was still present in about 80% of the eyes at the follow-up examination and the frequency of bouts of uveitis was reduced from about 6 to 1/year (*Gilger* et al. 2010). The leading causes of blindness had been persistent recurrences of uveitis, glaucoma, cataracts and retinal detachments. Because the recurrences of uveitis were the main reason for vision loss after a few years, it was recommended to place a new CsA device into the animal no later than 48 months after the first surgery. A concentration of CsA in the vitreous humour of 150–300 ng/ml (= 150–300 µg/l) was considered to be the effective therapeutic concentration.

Subsequently, 0.75 inch linear silicone matrix devices placed subconjunctivally (Table 1 and Figures 2 and 3) were used to treat horses with corneal and ocular surface diseases (Gilger et al. 2014, Gilger 2021). In this way, the sustained release of CsA hardly reaches the posterior segment of the eye, but there is assumed to be a sufficient CsA concentration to reduce corneal inflammations. The devices for the subconjunctival implantation would require several surgeries in a horse over its lifetime because there might be keratitis recurrences every 12–18 months.

The import of the CsA devices mentioned above is illegal in Germany. The only legal way for veterinarians to have these CsA devices would be by receiving exceptional approval from the authorities, which is not easy to get. Therefore, horses in Germany cannot normally have CsA implants. Despite these legally defined obstacles, however, several horses did get CsA implants and had been referred to the Equine Clinic of Ludwig-Maximilians University of Munich because of the CsA devices' lack of effectiveness to prevent ophthalmic problems.

Methods

Sixteen eyes (of 16 horses) which had been treated by an implantation of CsA devices previously are included in this study (Table 2), from which intraocular samples (either aqueous fluid or vitreous humour) could be taken. The history of these horses was documented. Ten of the 16 horses had suffered from leptospiral-induced ERU and were referred for vitrectomy because their CsA devices had not prevented ongoing bouts of uveitis. The CsA devices had been implanted 3 months up to more than 12 months prior to their referral (Table 2). In these horses, undiluted vitreous humour samples could be taken at the beginning of the vitrectomies. Another vitreous humour sample could be taken from one eye after enucleation. A CsA device had been implanted subconjunctivally in this eye five months earlier. Enucleation was indicated because the eye was blind, showed a severe atrophy of the globe and persistent pain. Two aqueous humour samples were taken from horses suffering from chronic heterochromic iritis which had not responded to the CsA implants. Aqueous sampling was indicated for exclusion or detection of an intraocular leptospiral infection. Three more aqueous samples were equally taken for diagnostic purposes from horses suffering from different types of chronic keratitis. All intraocular samples were sent to a laboratory (IHP, Institute for Haemostaseology and Pharmacology MVZ GmbH, Berlin-Steglitz) and tested for CsA using LC-MS/MS technology. The minimal detection limit was 10 µg/l (= 10 ng/ml). Eight of the 10 CsA implants in ERU eyes and 3 implants in eyes suffering from different types of keratitis were removed during surgery because they had not shown satisfactory efficacy, had irritated and caused corneal defects by rubbing the eye in one horse, or were too close to the sites for optimal laser sclerotomies in other horses.

Results

Location of the CsA devices

The CsA implant was correctly located between the sclera and the choroidea in only one of the ten horses with ERU. The remaining nine implants were located episclerally. One horse had received a second CsA implant four months after the insertion of the first, but this had also not led to the resolution of the recurrent uveitis. The CsA concentration was below the detection limit of 10 µg/l in all ten vitreous humour samples from the horses with ERU (Table 2). Regarding the CsA implants of the other six horses, the active substance carrier was located suprachoroidally in one horse suffering from chronic

Table 1 Literature review of sustained release cyclosporine A (CsA) devices used for the treatment of equine eye diseases | *Literaturüberblick über die bei Augenkrankheiten von Pferden verwendeten Cyclosporin A (CsA)- Wirkstoffträger mit prolongierter CsA-Abgabe*

Citation	Material	Indication	Site of implantation	Total amount of CsA	Expected daily release rate	Expected duration of release
Gilger et al. 1998 *Gilger* et al. 2001	CsA with silicone coating	recurrent uveitis	intravitreal	10 mg	4 µg/d	5 years
Gilger et al. 2006 *Gilger* et al. 2010	CsA in a polyvinyl alcohol polymer	recurrent uveitis	deep intrascleral or suprachoroidal	12 mg	initially > 23 µg/d, after day 30 about 6 µg/d	38 months (3.18 years)
Gilger et al. 2014 *Lee* et al. 2007	silicone matrix cyclosporine, CsA 30 %	chronic keratitis	episcleral/subconjunctival (release rate designed for human eyes)	12 mg (recommended: 2–4 pellets/horse)	initial five months: 2–5 µg/d, then > 1 year: 1–2 µg/d	12–18 months

keratitis (Figure 1) and subconjunctivally in each of the other five horses (Figures 2 and 3).

Laboratory results of intraocular fluid samples

Either antibodies directed against leptospires were detected and/or the PCR was positive (detection of LipL32) in all vitreous humour samples from eyes of horses with ERU. All other intraocular samples showed no evidence of an intraocular leptospiral infection. CsA was exclusively detectable in a single aqueous humour sample. This was the eye that had received three CsA implants subconjunctivally. The CsA concentration was 38.5 µg/l (= 38.5 ng/ml).

Clinical course after removal of the CsA implant and/or vitrectomy

No further episodes of uveitis occurred in the ten horses suffering from ERU for at least four years after vitrectomy, regardless of whether the CsA implant had been removed or not.

The three eyes suffering from chronic keratitis healed by vascularisation after the removal of the CsA implants. One horse had developed a corneal ulcer. In this horse, the CsA pellet was located suprachoroidally (Figure 1). However, CsA could not be detected in the aqueous fluid from this horse. The second horse suffered from keratitis associated with progressive corneal oedema. The intraocular pressure was always in the physiological range in repeated measurements. A tentative vascularisation in the cornea was visible ventrally, although three CsA implants had been inserted subconjunctivally four months earlier. This was the only horse in which the CsA was detectable in an intraocular sample (38.5 µg/l) (Table 2). After the removal of the CsA implants and vascularisation of the diseased corneal area, the oedema decreased progressively (Figures 4 and 5). In the end, only a smoky, line-shaped scar remained. The third horse showing chronic keratitis had received a CsA-releasing implant three years earlier. According to previous reports, no inflammation had occurred for 2.5 years after the operation, but the eye had been causing problems again for six months. Here, too, permanent healing was only possible after the ingrowth of blood vessels into the diseased and partly avital cornea.

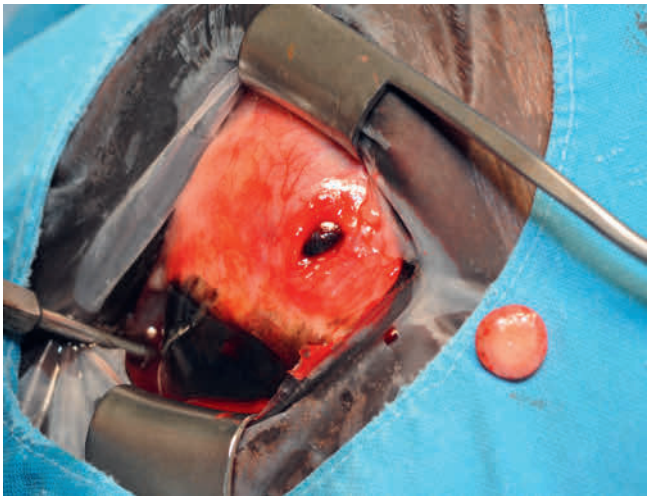

Fig. 1 Removal of the suprachoroidally placed CsA implant in a horse with chronic keratitis and development of a corneal ulcer | *Entfernung des suprachoroidal platzierten CsA-Implantats bei einem Pferd mit chronischer Keratitis und Entwicklung eines Hornhautulkus*

Two horses were suffering from chronic and non-leptospiral chronic iritis. Here again, the CsA implants had not led to any noticeable improvement. No CsA could be detected in either of these two aqueous humour samples (Table 2). As there was no evidence of a leptospiral infection in the aqueous humour samples of these horses, only continued symptomatic conservative therapy was possible.

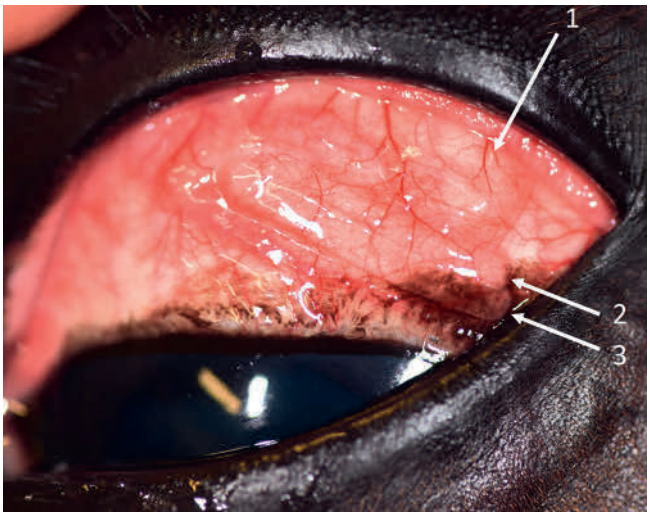

Fig. 2 Subconjunctival CsA implants. 1 = round CsA implant based on polyvinyl alcohol polymer (bioerodible), 2 and 3 = elongated implants with CsA in a silicone matrix | *Subkonjunktival liegende CsA-Implantate. 1 = rundliches CsA-Implantat auf Polyvinyl-Alkohol-Polymer-Basis (bioerodierbar), 2 und 3 = längliche Implantate mit CsA in einer Silikon-Matrix*

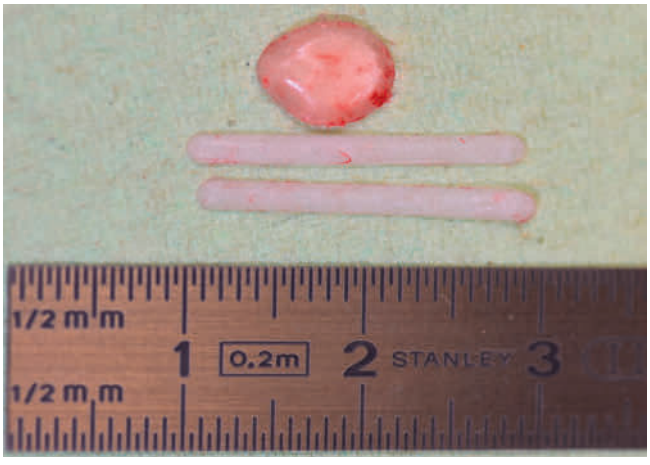

Fig. 3 The CsA-Implants from Figure 2 after their removal: two 0.75 inch linear silicone matrix implants for subconjunctival placement to treat corneal and ocular surface disease and one biodegradable matrix-reservoir CsA implant designed for suprachoroidal placement to treat ERU | *Die CsA-Implantate aus Abb. 2 nach deren Entfernung: zwei knapp 2 cm lange, längliche Silikonmatrix-CsA-Implantate, die subkonjunktival eingebracht werden sollen, um Hornhauterkrankungen zu behandeln und ein rundliches biologisch abbaubares Matrix-Reservoir CsA Pellet, das suprachoroidal eingebracht werden soll, um die ERU zu behandeln.*

Discussion

Vitrectomy has been described as an effective treatment for ERU for more than 30 years (*Werry* and *Gerhards* 1991, 1992, *Winterberg* and *Gerhards* 1997, *Frühauf* et al. 1998, *Gerhards* et al. 1998, *Gerhards* et al. 1999, *Wollanke* et al. 2004, *von Borstel* et al. 2005, *Tömördy* et al. 2010, *Dorrego*-Keiter et al. 2017, *Schinagl* 2017, *Baake* et al. 2019, *Voelter* et al. 2020). However, vitrectomy is a demanding surgery which has a a relative long learning curve. Increasing experience with this surgery will lead to fewer complications. Any complications or minor surgical misfortunes during an intraocular surgery may lead to blindness due to, for example, cataract formations, retinal detachments or severe intraocular haemorrhage and in some circumstances to intraocular infection. In addition to experience with the surgical procedure of the surgeon and the sterile and unsterile assistants, expensive equipment, including customised instruments which meet the requirements of the dimensions of equine eyes, are indispensable. Finally, careful establishment of an indication for this intraocular surgery is crucial to obtain the results described (*Gerhards* and *Wollanke* 2005, *Schinagl* 2017).

These points which can severely affect the results of vitrectomies might have led to the development and frequent application of CsA devices in horses suffering from ERU and, subsequently, also in horses suffering from different forms of chronic keratitis (*Gilger* et al. 2010, *Gilger* et al. 2014). Furthermore, eyes with intraocular leptospiral infections initially had been excluded from the implantation of CsA devices (*Gilger* et al. 1998). However, testing serum for agglutinating antibodies, which has been used to exclude leptospiral uveitis, is not a suitable method for diagnosing an intraocular leptospiral infection (*Wollanke* et al. 2004).

The CsA implants for this application can still be obtained from the NC State Veterinary Hospital (Raleigh, North Carolina, USA) (*Gilger* 2021), which sends them internationally, independent of legal restrictions at the destination. However, the implant is an experimental device or procedure that has not been approved by the competent authority (FDA, Food and Drug Administration) for use in horses in the United States: "Clinical studies in horses with ERU have shown excellent control of the disease. However, this is an experimental device and not approved for use in horses by the FDA". Moreover, suprachoroidal sustained release CsA devices are not regarded as a sophisticated and innovative eye treatment system in human medicine (*Mazet* et al. 2020).

In this study, 15 of 16 horses had no measurable CsA concentration in their intraocular fluids. The CsA implant was found to be subconjunctival instead of suprachoroidal in most ERU-eyes. This might be an explanation for the lack of CsA in the intraocular fluids. Nevertheless, the implant was located suprachoroidally in two eyes and there was no CsA detectable in the intraocular fluid samples. Surprisingly, the only horse with a detectable concentration of CsA in its aqueous fluid had been treated with three CsA devices in place, although they were located subconjunctivally. However, the concentration (38.5 µg/l) was below commonly accepted therapeutic levels of 150-300 µg/l (*Gilger* et al. 1998, *Gilger* et al. 2000). None of the eyes showing any kind of uveitis had responded to the CsA treatment as intended, however, the CsA implantation had been performed in only one of these eyes correctly by placing the device suprachoroidally. This might have contributed to the lack of effectiveness, and therefore, misplacing CsA implants like this may represent sham operations. Despite the absence of a detectable concentration of CsA in the aqueous fluid, there might have been a healing delaying CsA effect in the horse suffering from corneal defects and, finally, ulceration of the cornea. It was only after the removal of the CsA implant

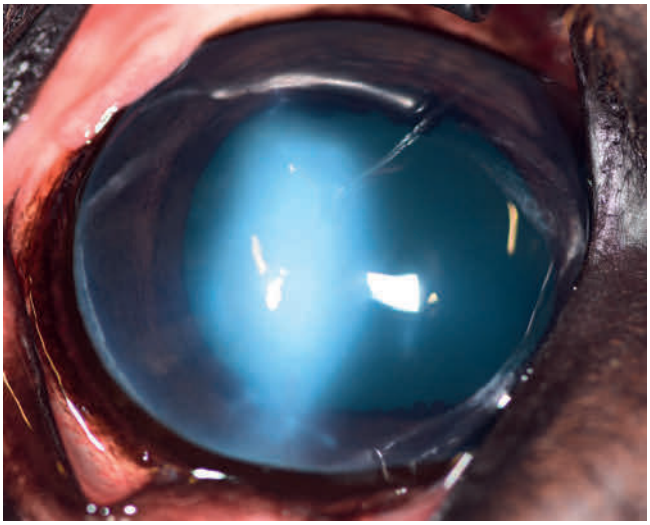

Fig. 4 Corneal oedema of the horse that had three subconjunctival CsA implants on admission. The tentative vascularisation present at "6 o'clock" is not visible on the picture due to the oedema | *Hornhautödem des Pferdes, das die 3 subkonjunktival liegenden CsA-Implantate hatte, bei Einlieferung. Die bei „6 Uhr" vorliegende zaghafte Vaskularisation ist auf dem Bild durch das Ödem nicht zu erkennen*

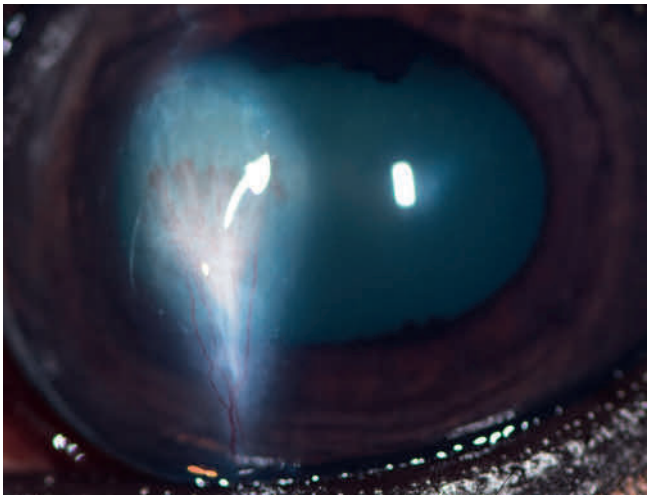

Fig. 5 Condition of the cornea from Figure 4 after a few weeks. After removal of the CsA implants, the vascularisation of the cornea has progressed continuously. The oedema has decreased more and more with the vascularisation. According to the owner, only a line-shaped scar remained and no further treatment of the eye was necessary since discharge from the clinic | *Zustand der Hornhaut aus Abb. 4 nach wenigen Wochen. Nach Entfernung der CsA-Implantate ist die Vaskularisation der Hornhaut kontinuierlich fortgeschritten. Mit der Vaskularisation ist das Ödem immer weiter zurückgegangen. Laut Auskunft des Besitzers ist zuletzt lediglich eine strichförmige Narbe zurückgeblieben und eine weitere Behandlung des Auges war seit Entlassung aus der Klinik nicht mehr erforderlich*

Table 2 Underlying diseases of the examined equine eyes, clinical course after inserting of the cyclosporine A (CsA) implants and measuring the CsA-concentration in the intraocular samples. WB = warmblood, y. = years. Aqu = aqueous, Vit = vitreous humour | *Grunderkrankungen der untersuchten Pferdeaugen, Verlauf nach Einsetzen der Cyclosporin A (CsA)-Implantate und Bestimmung des CsA-Gehalts in den intraokularen Proben. WB = Warmblut, y. = Jahre, Aqu = Kammerwasser, Vit = Glaskörper*

disease	no.	horses	cyclosporine implant since	clinical findings after implanting the cyclosporine pellet	location of the implant	cyclosporine concentration (sample)	others
ERU	1	12 y. gelding, Trotter	3 months	1 more ERU-attacks	episcleral	< 10µg/l (Vit)	irritation by the pellet
	2	1 y. mare, WB	4 months	2 more ERU-attacks	episcleral	< 10µg/l (Vit)	
	3	11 y. WB mare	4 months	3 more ERU-attacks	suprachoroidal	< 10µg/l (Vit)	
	4	8 y. gelding, Thoroughbred	7 months	2 more ERU-attacks	episcleral	< 10µg/l (Vit)	
	5	10 y. gelding, WB	9 months	4 more ERU-attacks	episcleral	< 10µg/l (Vit)	
	6	7 y. gelding, pony	10 months	3 more ERU- attacks	episcleral	< 10µg/l (Vit)	pellet kept for 4 weeks in BSS®, afterwards > 1400µg CsA/l BSS®
	7	6 y. gelding, Thoroughbred	14 and 10 months	3 more ERU-attacks since deploying the cyclosporine pellets	episcleral	< 10µg/l (Vit)	2nd cyclosporine pellet when the 1st was ineffective
	8	16 y. gelding, WB	11 months	3 more ERU- attacks	episcleral	< 10µg/l (Vit)	
	9	6 y. gelding, WB	> 9 months	2 ERU- attacks since purchase	episcleral	< 10µg/l (Vit)	puchased 9 months ago, no knowledge about the implant
	10	6 y. stallion, WB	unknown	3 ERU-attacks within 6 weeks	episcleral	< 10µg/l (Vit)	
chronic keratitis	11	6 y. stallion, Thoroughbred	5 months	no healing, defects at first, then ulceration	suprachoroidal	< 10µg/l (Aqu)	
	12	10 y. gelding, WB	6 months	increasing corneal edema, very little vascularisation	episcleral	35.5µg/l (Aqu)	a total of 3 CsA-implants; kept for 1 week in BSS®, afterwards > 3000µg CsA/l BSS®
	13	11 y. mare, WB	3 years	2,5 years fine, then inflammations again	episcleral	< 10µg/l (Aqu)	
chronic keratitis and uveitis, blind	14	12 y. mare, WB	5 months	ongoing inflammations	episcleral	< 10µg/l (Vit)	sampling after enucleation
chronic iritis	15	12 y. mare, WB	12 months	1 more inflammation, then daily topical prednisolone	episcleral	< 10µg/l (Aqu)	
	16	10 y. mare, pony	unknown	chronische Iritis	episcleral	< 10µg/l (Aqu)	

that vascularisation and healing of the cornea occurred. The third horse suffering from chronic keratitis showed problems again after the CsA release had probably ceased.

It can be concluded that CsA has an effect on chronic keratitis, but prevention of the ingrowth of vessels into the cornea might mean a disadvantage or even pose a danger to the eye. To the best of the authors' experience, vascularisation of the cornea is the most effective treatment option and provides the best long-term results in recurrent and chronic keratitis. Thus, if the initial and perhaps repeatedly performed topical anti-inflammatory treatment using, for example, dexamethasone ointments does not provide lasting success, measures to promote corneal vascularisation are the most sustainable treatment options.

Regardless of the clinical aspects and the restrictions concerning the pharmaceutical law (legal prohibition of import of CsA devices), the German Animal Protection Act also has to be considered. This law says in § 3 (1a) that it is prohibited to demand any performances from an animal on which interventions and treatments have been carried out which conceal a performance-reducing physical condition, which the animal is not up to due to its physical properties (TSG 2021). On the other hand, surprisingly, the German national equestrian association "FN" explicitly excludes CsA implants from prohibited substances and, thus, allows horses which carry a CsA implant to participate in tournaments (FN ADMR 2021). These contradictions are incomprehensible.

Some recent studies compare the effects of CsA devices and vitrectomy. Additionally, follow-up studies after the implantation of CsA devices can be compared with those after vitrectomy. Based on this comparison, vitrectomy has been proven to be far superior to sustained-release CsA implants regarding the occurrence of bouts of uveitis as well as the long-term results regarding the preservation of vision (*Tömördy* et al. 2010, *Schinagl* 2017, *Waid* et al. 2018, *Baake* et al. 2019, *Voelter* et al. 2020).

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