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Ocular Pharmacokinetics and Safety of Ciclosporin, a Novel Topical Treatment for Dry Eye

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Abstract

Ciclosporin is a potent immunomodulator that acts selectively and locally when administered at the ocular surface. 0.05% ciclosporin ophthalmic emulsion has recently been approved by the US FDA for treatment of keratoconjunctivitis sicca (KCS) [dry-eye disease].

After topical application, ciclosporin accumulates at the ocular surface and cornea, achieving concentrations (≥0.236 μg/g) that are sufficient for immunomodulation. Very little drug penetrates through the ocular surface to intraocular tissues. Ciclosporin is not metabolised in rabbit or dog eyes and may not be prone to metabolism in human eyes. Cultured human corneal endothelial and stromal cells exposed to ciclosporin *in vitro* exhibited no adverse effects and only minor effects on DNA synthesis. No ocular or systemic toxicity was seen with long-term ocular administration of ciclosporin at concentrations up to 0.4%, given as many as six times daily for 6 months in rabbits and 1 year in dogs. Systemic blood ciclosporin concentration after ocular administration was extremely low or undetectable in rabbits, dogs and humans, obviating concerns about systemic toxicity. In 12-week and 1-year clinical safety studies in dry-eye patients, the most

common adverse event associated with the ophthalmic use of ciclosporin emulsion was ocular burning. No serious drug-related adverse events occurred.

These data from *in vitro*, nonclinical and clinical studies indicate effective topical delivery of ciclosporin to desired target tissues along with a favourable safety profile, making 0.05% ciclosporin ophthalmic emulsion a promising treatment for KCS.

Ciclosporin is a potent immunomodulator that has been used to treat various immunological disorders for more than two decades.[1] The drug was first introduced for prevention of solid organ graft rejection in 1983.[2] In addition to its applications for immunosuppression after transplantation and for treatment of rheumatoid arthritis and severe psoriasis, systemically administered ciclosporin at dosages from 2 to 15 mg/kg/day has been found to relieve many ocular disorders such as uveitis, Behçet's disease and bird shot retinochoroiditis.[3-8] Common adverse effects associated with systemic administration of ciclosporin, including elevated serum creatinine, hypertension and renal dysfunction, are reversed upon reduction of the ciclosporin dosage.[4] Such adverse effects limit systemic ciclosporin use to the treatment of intraocular disorders unlikely to respond to topically administered therapies.

For ocular surface disorders, delivery of ciclosporin directly to the eye provides efficacy and safety advantages. Treatment by topical administration achieves high ciclosporin concentrations in surface tissues and precludes toxicity associated with high systemic levels of ciclosporin. Ophthalmic application of ciclosporin has been used for corneal allografts,[9] vernal keratoconjunctivitis,[10] keratoconjunctivitis sicca (KCS) [dry-eye disease],[11] immune-mediated keratitis,[12] necrotising scleritis[13] and herpetic stromal keratitis.[14] 0.05% ciclosporin ophthalmic emulsion has been evaluated for treatment of KCS in several large clinical trials.[15,16]

Dry-eye patients exhibit chronic inflammation at the ocular surface and in the lacrimal gland.[11,17] Immunohistochemical studies have demonstrated accumulation of CD4 (T-helper) cells within these tissues.[18,19] Ciclosporin specifically inhibits the activation of T-helper cells in the ocular surface tissues by blocking the production of interleukin-2, a key cytokine for immune-mediated inflammation.[20] Topical ophthalmic ciclosporin has been shown to reduce lacrimal gland lymphocytic infiltrates and improve tear production in dry-eye patients with or without Sjögren's syndrome[21-24] and in dogs with dry eye.[25-28]

In 1995, the US FDA approved 0.2% ciclosporin ophthalmic ointment (Optimmune®; Schering-Plough, Union, NJ, USA)[1] for the treatment of canine KCS. Various vehicles have been tested for ocular penetration in rabbits and in humans, including castor oil,[29] aqueous cyclodextrin,[30] collagen shields,[31] nanocapsules,[32] nanoparticles[33] and emulsions.[34] Recently, the FDA approved Restasis™ 0.05% ophthalmic ciclosporin emulsion (Allergan, Irvine, CA, USA) for treatment of KCS in humans. It is the first commercially available therapy that acts on the inflammation underlying KCS.

This review explores ocular pharmacokinetics and safety studies of ciclosporin, as well as drug bioavailability in formulations tested during development of 0.05% ciclosporin emulsion.

1. Physicochemical Properties and Ophthalmic Dosage Forms

Ciclosporin is a neutral, hydrophobic, cyclic undecapeptide[35] (figure 1) with a molecular weight of 1202.6 daltons. Given its physicochemical properties, ciclosporin presents a challenge in developing an ophthalmic formulation of adequate drug concentration to provide stability, reliable drug delivery and acceptable vehicle safety. Topical drug absorption is a function of formulation, drug concentration and vehicle drug solubility. The poor water solubility of ciclosporin should preclude aqueous solution formulations for any clinically useful dosage strength, but ciclosporin suspensions in balanced

1 The use of trade names is for product identification purposes only and does not imply endorsement.

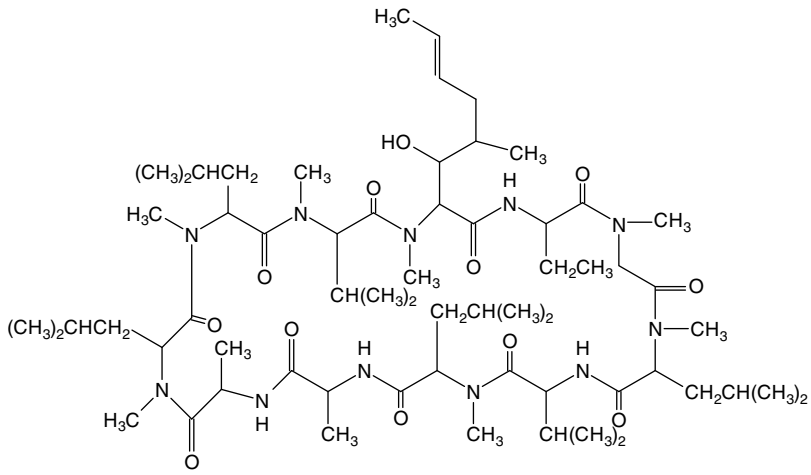

Fig. 1. Chemical structure of ciclosporin.

salt solution,[36] in aqueous cyclodextrin solution[30] and in polyisohexylcyanoacrylate nanocapsules dispersed in an isotonic and neutral aqueous vehicle are under investigation.[37,38] Many ophthalmic ciclosporin dosage forms have been prepared in castor, corn, olive and peanut oils. However, epithelial keratitis has been associated with the use of these oil vehicles.[36,39] While ciclosporin formulated in a corn oil ointment helped relieve symptoms of KCS patients, it was also associated with early burning, redness and itching.[22]

To improve delivery of ciclosporin to ocular tissues, an emulsion formulation in castor oil was developed that produces sustained ciclosporin concentrations sufficient for immunomodulation in external ocular tissues. Using this emulsion formulation, ciclosporin concentrations as low as 0.05% effectively treated symptoms of dry-eye disease.[15,16] Topical administration of the castor oil-water emulsion results in extremely low systemic ciclosporin concentrations while maintaining acceptable patient comfort. The castor oil-water emulsion formulation used for Restasis™ also includes glycerin, polysorbate 80 and sodium hydroxide to adjust the pH.[40] Upon instillation directly into the eyes, ciclosporin partitions from the oil droplets into ocular surface tissues (see section 3.1). The ocular retention time (ORT) for this emulsion vehicle is approximately 2 hours,[41] which exceeds that observed for saline and viscous solution formulations (in the range of minutes).[42]

2. Bioanalytical Methodology

Treatment by topical administration of ciclosporin avoids toxicity associated with high systemic levels of ciclosporin. Because topical administration of ciclosporin results in extremely low blood concentrations (section 3.1), highly sensitive and selective detection methods are required. Many bioanalytical methods have been developed to assay ciclosporin in human blood.[16,43-48] Among these methods, radioimmunoassay (RIA) and fluorescence polarisation immunoassay (FPIA) provide rapid means for determining ciclosporin concentrations in biological fluids; however, both methods generally tend to overestimate ciclosporin concentration because of cross-reactivity with its many metabolites. High pressure liquid chromatography (HPLC) appears to be more selective than RIA and FPIA. None of these methods, however, are very sensitive; the lower limits of quantitation (LLOQ) for RIA, FPIA and HPLC were 62.5, 50 and 20 μg/L, respectively.[45] Several more sensitive liquid chromatography-mass spectrometry (LC-MS/MS) methods have been developed for the assay of ciclosporin in human blood, providing LLOQ in the range of 0.5–10 μg/L.[43,44,46]

An even more sensitive LC-MS/MS method has been developed for the determination of ciclosporin

Table I. Ciclosporin concentrations (ng/g or ng Eq/g) in ocular tissue after ocular administration in laboratory animals

Formulation	Regimen	No. of eyes	Conjunctiva	Cornea	Lacrimal gland	Aqueous humour	Iris-ciliary body lens	Anterior uvea	Vitreous humour	Retina	Blood	Reference
Rabbits												
1% in olive oil	1 drop (7μL) q15min × 6	6		4000	2850	20		180	50	150	BLQ	49
10% in petrolatum ointment	One 2cm ribbon	6		926 ± 384		168 ± 184					87 ± 153 serum	50
2% in olive oil	1 drop (100μL) bid for 5 days	20		261 ± 60							56 ± 24	51
2% in olive oil	1 drop (100μL) qid for 10 days	20		1111 ± 449							89 ± 60	51
2% in castor oil	1 drop (10μL)	6		900–1400		25–45			8.0–20	7.0–18		29
2% in olive oil	1 drop tid for 7 days	12, normal	100	90		BLQ					BLQ	52
2% in olive oil	1 drop tid for 7 days	12, uveitis	100	90		100	40				BLQ	52
1% in olive oil	1 drop, 5 × daily for 4wk, then qid or bid until 6mo	7				91–254					60–233 plasma	53
0.8% in nanocapsules	1 drop (7μL) q15min × 6	6		1400		200			150	800		38
0.2% emulsion[a]	1 drop (35μL)	6	1230	751	37	7	68					58
0.05% emulsion[a]	1 drop (50μL) bid for 9.5 days	20	713	1550	12	1.4				<0.7		54
0.1% emulsion[a]	1 drop (50μL) bid for 9.5 days	20	1920	4810	15	7.1				<1.9		54
0.5% solution	1 drop (35μL) q15min × 4	4	6920	9410		<59						55
Dogs												
0.2% emulsion[a]	1 drop (35μL) bid for 7 days	7	2007	1809	357	0.6	36			1.2		56
0.5% solution	1 drop (35μL) q15min × 4	4	3100	3840		<59						55

a Castor oil-water emulsion.

bid = twice daily; **BLQ** = below limit of quantitation; **qid** = four times daily; **q15min** = every 15 minutes; **tid** = three times daily.

concentrations in human and dog blood.[16] A similar assay was used for rabbit blood. An organic extract of each blood sample was characterised by separation on a reverse-phase HPLC column coupled to a mass spectrometer. Protonated molecules of ciclosporin (m/z 1203) and geclosporin (m/z 1217), the internal standard, were collisionally dissociated; product ions at m/z 425 were monitored. Standard curves for human and dog assays were linear over the concentration range of 0.1–5 μg/L. Interday precision (percentage relative standard deviation) based on day-to-day evaluation of quality control samples of human or dog blood was <14%. Interday accuracies for the human blood and dog blood assays were 102.6–113.4% and 94.6–108.3%, respectively. The LLOQ was 0.1 μg/L, providing greater sensitivity than HPLC, RIA, FPIA or earlier LC-MS/MS methods.

3. Pharmacokinetics of Ophthalmic Ciclosporin

3.1 Ocular Absorption and Distribution

3.1.1 Animals

Ocular absorption and tissue distribution of ciclosporin after ophthalmic administration have been studied extensively in rabbits and dogs.[29,38,41,49-56] Results of these studies are consistent in two respects: high ciclosporin bioavailability is observed for ocular surface tissues, and drug penetration into intraocular tissues is extremely poor (table I and table II). After topical instillation, ciclosporin readily leaves the tear film and partitions into the conjunctiva, cornea and accessory lacrimal glands, achieving high concentrations. Cyclosporin concentrations in the conjunctiva, cornea and lacrimal gland of rabbits increased as the ciclosporin strength in the castor oil-water emulsion increased from 0.05% to 0.2% (table I). In general, these concentrations of ciclosporin in ocular tissues were observed 20 minutes to 1 hour after dose instillation, indicating that ciclosporin was rapidly absorbed into rabbit and dog eyes.[57]

The corneal epithelium is the most significant drug reservoir for topically applied ciclosporin in rabbits.[29] The corneal stroma, however, is mainly composed of water and is an effective barrier against penetration of ciclosporin from the castor oil-water emulsion, resulting in sustained high concentrations at the ocular surface and low concentrations in intraocular tissues (table II).

The absorption, efficacy and potential toxicity of a drug can each increase with repeated administration. Ratios in various ocular tissues of the maximum concentration (C_{max}) values after multiple ocular doses to those after single ocular doses were determined to estimate the extent of ciclosporin accumulation after repeated administration of a castor oil-water emulsion formulation.[41] These ratios showed variable accumulation of ciclosporin in different ocular tissues of dogs and rabbits. In dogs, ciclosporin accumulated slightly in the conjunctiva (multiple-dose/single-dose ratio 1.4), moderately in the lacrimal gland (ratio 2.4), and to a greater extent in the cornea (ratio 5.8). In rabbits, ciclosporin accumulated moderately in the cornea (ratio 3.9) and significantly in the lacrimal gland (ratio 9.2). The relative accumulation of ciclosporin in various tissues was similar in rabbits and dogs; the difference seen in the accumulation ratios for the lacrimal gland was attributed to anatomical differences between the two species.[41] Work by Kaswan et al.[25,26,49] showed that the dog is better than the rabbit for modelling ciclosporin penetration and efficacy in humans.

Drug vehicle retention time is a major factor affecting the extent of a drug's accumulation. Studies were conducted in the left eyes of beagle dogs to evaluate the ORT of the ciclosporin castor oil-water emulsion formulations and corresponding vehicles.[41] The castor oil content of the emulsion was elevated for formulations containing greater ciclosporin concentrations. The mean ORT after instillation increased proportionately with increasing ciclosporin concentration (and increasing castor oil content). For example, 0.05% ciclosporin had an ORT of 1.75 hours, whereas 0.2% ciclosporin had an ORT of 3.1 hours. Similarly, the vehicle for 0.05% ciclosporin had an ORT of 2 hours and the vehicle for 2% ciclosporin had an ORT of 2.75 hours. The long ORTs may have contributed to the prolonged absorption of ciclosporin into ocular surface tissues. In clinical terms, the emulsion vehicle may reduce evaporation of the limited natural tears

Table II. Ciclosporin concentrations in various tissues after ocular administration of 0.05% ciclosporin emulsion formulation

Tissue	Maximum concentration (ng/g)	
	rabbit[54]	dog[a][41]
Tears	14 000	7183
Cornea	1550	452
Conjunctiva	643	502
Sclera	84.5	31.3
Lacrimal gland	11.9	89.3
Aqueous humour	1.44	0.158
Iris-ciliary body	74.7	8.93
Lens	18.4	0.76
Vitreous humour	2.93	0.07
Choroid-retina	95.3	3.0

a Data extrapolated from 0.2% ciclosporin administration.

produced by patients with dry-eye disease, thereby providing additional benefits to these patients.

The terminal half-life of ciclosporin in ocular tissues after ocular administration was long,[41] approximately 40 hours in rabbit corneas and 20–30 hours in the conjunctivae of rabbits and dogs. Such prolonged retention of ciclosporin, together with the favourable drug partitioning into the ocular surface tissues discussed earlier in this section, promotes prolonged ciclosporin efficacy in the ocular surface tissues associated with dry-eye disease.

3.1.2 Humans

More studies of ciclosporin concentrations in ocular tissue and blood have been performed for laboratory animals (section 3.1.1) than for humans; in addition, the results from the few clinical trials are much more variable. After topical application of ciclosporin (0.5% in olive oil), an extremely steep concentration gradient (over two orders of magnitude) formed across the human cornea button; ciclosporin concentrations of 1.252, 0.161 and 0.007 ng/mm^2 accumulated in the epithelium, stroma and endothelium, respectively.[59] Low aqueous humour concentrations in clinical studies showed that intraocular penetration of ophthalmic ciclosporin was low (mean values <100 μg/L) [table III]. These results are consistent with observations in laboratory animal eyes (table I).

Ciclosporin concentrations in human cornea and conjunctiva after instillation of 0.05% ciclosporin emulsion are not available, but may be extrapolated from tissue concentration data in rabbits and dogs treated with 0.05% ciclosporin emulsion. Human[61] and dog[55] corneal concentrations were similar (3840 ng/g vs 3700 ng/g) after ocular instillation of a 0.5% aqueous solution of ciclosporin every 15 minutes for 1 hour before keratoplasty. When albino rabbits received an identical dosage regimen and formulation, the mean corneal concentration was approximately 9400 ng/g.[55] These data indicate that when rabbits, dogs and humans are subjected to the same ciclosporin ophthalmic regimen, human corneal concentrations are comparable to those in dogs and 40% of those in rabbits. Therefore, based on a steady-state corneal C_{max} value of 1550 ng/g during 0.05% ciclosporin emulsion treatment twice daily to rabbits,[54] the human corneal C_{max} value should be 620 ng/g. The steady-state C_{max} value in dog cornea[41] (452 ng/g) comes close to that value.

Choice of vehicle can affect the drug's availability. In the study where 0.5% ciclosporin was administered in aqueous solution,[61] the mean human corneal ciclosporin concentration was approximately 3700 ng/g. Topical instillation of five to ten drops of 2% ciclosporin solution in olive oil yielded a mean human cornea ciclosporin concentration of only 236 ng/g.[65] This low corneal concentration occurred despite the greater drug concentration, and despite the initiation of treatment 1 day before keratoplasty, as opposed to 1 hour before keratoplasty for the 0.5% ciclosporin in aqueous solution. Olive oil is clearly a less favourable vehicle for delivery of ciclosporin than castor oil.

3.2 Ocular Metabolism

Although extensive metabolism of ciclosporin occurs in the livers of humans and laboratory animals,[66] ciclosporin is not metabolised in rabbit eyes[29,41] or in dog eyes.[57]

On the basis of these observations, ocular metabolism of ciclosporin is not expected in humans. In one study, hydroxylated ciclosporin metabolites were detected in the aqueous humour of patients who received one to two drops of 2% ciclosporin prior to cataract surgery.[60] Ciclosporin is mainly metabolised by hepatic cytochrome P450 (CYP) 3A isoenzymes[67] whose ocular metabolic activities are 1000–5000 times lower than those found in hepatic microsomes. These data, together with observations that constitutive CYP drug metabolism activities in rabbit, dog, monkey and human eyes are qualitative-

Table III. Ciclosporin concentrations (ng/g or μg/L) in ocular tissue and blood after ocular administration of ciclosporin in humans

Formulation	Regimen	No. of eyes	Blood	Cornea	Conjunctiva	Aqueous humour	Method	Reference
2% in oil	1 drop	28				95 ± 140	LC-MS	60
2% in oil	1 drop	21				62 ± 54	LC-MS	60
0.5% solution	1 drop q15min	9		3687 ± 1077		6.1	LC-MS/MS	61
0.5% suspension		9	<50	343–450		<50	LC-MS	59
2% in peanut oil	1 drop tid for 3 days	10	4.7		10 ± 10	33 ± 45	RIA	62
2% in olive oil	2 drops q6h × 4	30				23.7 ± 9.8	FPIA	63
2% in olive oil	2 drops q6h × 4 plus collagen shield	30				42.9 ± 10.1	FPIA	63
2% in olive oil	2 drops q6h	30	BLQ			24	FPIA	64
2% in olive oil		7		236 ± 42			FPIA	65
2%	1 drop 5 times in 1 day	8	BLQ			17 ± 7	FPIA	65
2%	2 drops 5 times in 1 day	14	BLQ			25 ± 9	FPIA	65

BLQ = below limit of quantitation; **FPIA** = fluorescence polarisation immunoassay; **LC-MS** = liquid chromatography/mass spectroscopy; **q15min** = every 15 minutes; **q6h** = every 6 hours; **RIA** = radioimmunoassay; **tid** = three times daily.

ly similar,[68] suggest that little or no ocular metabolism of ciclosporin occurs in humans. Thus, drug interactions due to metabolic mechanisms are not expected from ophthalmic ciclosporin treatment.

3.3 Ocular and Systemic Cyclosporin Concentrations in Humans

Ocular ciclosporin concentrations observed after ophthalmic ciclosporin application are much lower than the systemic tissue ciclosporin concentrations required for procedures such as organ transplantation. In patients with (n = 8) and without (n = 9) cellular rejection after orthotopic liver transplantation, a statistically significant difference occurred in hepatic ciclosporin concentrations (1879 ± 998 vs 3493 ± 936 ng/g; $p < 0.01$), suggesting a threshold concentration for immunosuppression.[69] Similar observations were reported for kidney,[70] ileum[71] and colon.[69,72] Patients whose systemic treatment with ciclosporin resulted in successful immunosuppression had mean tissue concentrations ranging from 3000 to 10 000 ng/g (figure 2). These concentrations are 8- to 20-fold greater than the ciclosporin concentrations in ocular surface tissues (estimated to be 450–620 ng/g, extrapolated from dog and rabbit data) anticipated from topical application of ophthalmic 0.05% ciclosporin emulsion in dry-eye patients. When administered topically, 0.05% ciclosporin castor oil-water emulsion has been shown to alleviate symptoms of KCS.[15,16]

4. Ocular Safety of Ciclosporin

4.1 *In Vitro* Studies

Ophthalmic administration of ciclosporin is a possible way to avoid adverse effects associated with systemic administration, such as elevated serum creatinine, hypertension and renal dysfunction.[73] To evaluate whether ophthalmic administration of ciclosporin is safe, ciclosporin toxicity was tested on cultured human corneal endothelial monolayer from a 9-month-old donor. These cells showed signs of proliferation, elongation and mitosis, with normal nuclei and no vacuolisation of the cell cytoplasm. After treatment of cells by addition of up to 1000 μg/L ciclosporin to the culture medium for up to 7 days, no degenerative vacuoles appeared in the

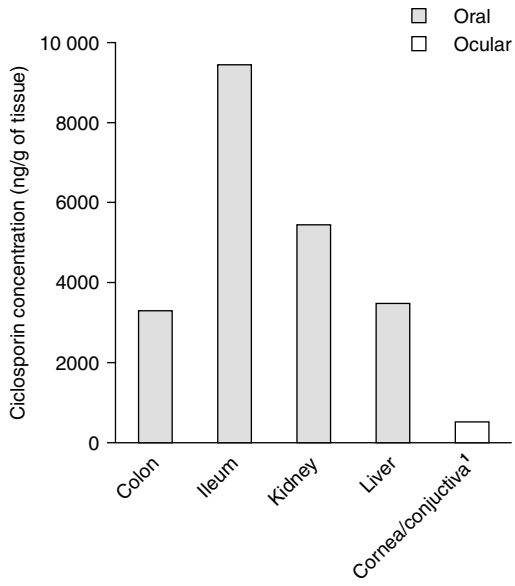

Fig. 2. Comparative human tissue ciclosporin concentrations. Concentrations in colon, ileum, kidney and liver are from immunosuppressive treatment by oral or intravenous administration of ciclosporin,[69-71] whereas the concentration in cornea/conjunctiva represents ocular administration of 0.05% ciclosporin in castor oil emulsion. **1** Ciclosporin concentration in cornea and conjunctiva is predicted from comparable data sets in rabbit, dog and human.

cytoplasm. The cells maintained normal morphology and showed mitotic cell divisions similar to those of untreated control cells.[74] Additionally, no adverse effects occurred in corneal stroma cell cultures exposed to higher concentrations of ciclosporin, from 100 to 250 μg/mL;[75] however, DNA synthesis in cultured epithelial cells was minimally decreased (10–15%) under these conditions.

4.2 Animal Studies

4.2.1 Topical Administration

The ocular safety of ciclosporin ophthalmic castor oil-water emulsions was evaluated by long-term ocular studies in rabbits and beagle dogs.[76] Ciclosporin ophthalmic formulations did not produce any ocular toxicity at concentrations up to 0.4% administered as many as six times daily for up to 6 months in rabbits and for up to 1 year in dogs; also, there were no ciclosporin-related histological changes in the eye.

Dogs with spontaneous KCS have a high incidence of ocular surface infection. When KCS dogs were treated with 2% ciclosporin twice daily for up to 1 year, there were no opportunistic corneal infections,[77] further supporting the safety of ocular use of ciclosporin.

4.2.2 Systemic Administration

Long-term oral toxicity studies of ciclosporin have been conducted in mice, rats and dogs. In three mouse and rat studies where ciclosporin was given orally, there were no macroscopic or microscopic eye findings, nor was there any evidence of toxicity-related pre-neoplastic or neoplastic events in the eye. At the same time, the dosages yielded serum and tissue concentrations sufficient for drug efficacy. Oral ciclosporin administration produced serum ciclosporin levels in the immunosuppressive range, up to 200 μg/L in mice[78] and up to 120–350 μg/L in rats.[79] In a similar 104-week study of oral administration in rats,[80] corneal ciclosporin concentrations ranged from 200 to700 ng/g for a 2 mg/kg/day group and from 500 to 900 ng/g for an 8 mg/kg/day group; corresponding conjunctival ciclosporin concentrations ranged from 700 to 2000 ng/g and from 1500 to 3000 ng/g.

In several long-term canine studies, oral ciclosporin dosages resulted in high concentrations in plasma and in tissues, but no ocular toxicity. Dogs given ciclosporin orally had plasma ciclosporin concentrations up to 5242 μg/L after 52 weeks.[79] In a similar study, dogs had corneal ciclosporin concentrations of 335 μg/L for a 15 mg/kg/day group and 2123 μg/L for a 45 mg/kg/day group, with corresponding conjunctival ciclosporin concentrations of 1296 and 4616 μg/L. Corresponding lacrimal gland ciclosporin concentrations were 13 028 and 9871 μg/L.[80] No ocular toxicity was observed in these canine studies, supporting the long-term ocular safety of ciclosporin.

4.3 Oral Administration in Humans

Many clinical trials have evaluated oral ciclosporin treatment of humans for ocular inflammation and immunological disorders (table IV). From 1984 to 1996, more than 550 patients used oral ciclosporin for periods of up to 44 months for treatment and up to 8 years of continuous follow-up,

with only a handful of adverse events requiring the discontinuation of treatment. Of these, not one was related to the eye: four cases involved nephrotoxicity, three systemic hypertension, three nausea/malaise, and one gingivitis.

Among these studies, three were randomised, double-blind clinical trials. In a 1-year comparative, prospective trial of 56 patients with endogenous uveitis (excluding Behçet's disease), patients received either ciclosporin 10 mg/kg/day (initial dosage) or prednisolone.[3] Although the ciclosporin group complained of more adverse effects, no complaints were related to the eyes and all were resolved with dose reduction.

In a second trial, 27 patients received either ciclosporin (10 mg/kg/day initially, with tapering over 1 year) plus prednisone, or placebo plus prednisone.[81] The ciclosporin group initially performed better than the placebo group, but the positive effect diminished as the dosage was reduced. The investigators concluded that ciclosporin was effective and may be considered in the treatment of uveitis. All adverse effects were systemic in nature and no ocular adverse effects were reported.

In a comparative trial of ciclosporin versus colchicine followed by an open-label extension, 96 patients with Behçet's disease received either ciclosporin 10 mg/kg/day or colchicine 1 mg/day and were followed up for 16 weeks.[6] Weekly assessments included visual acuity, ocular manifestations (by slit-lamp microscopy, tonometry and funduscopy), systemic symptoms and the frequency of ocular attack. Ciclosporin produced improvement in 91% of patients with minimal adverse effects, whereas only 33% of colchicine-treated patients improved. The most serious adverse effect was renal dysfunction.

Results from other studies including uncontrolled prospective trials, retrospective chart reviews, and case studies (table IV) were generally consistent with those from the three randomised, double-blind studies.[3,6,81]

5. Systemic Drug Exposure and Safety after Topical Administration

5.1 Animals

Systemic drug exposure and safety after administration of ophthalmic ciclosporin castor oil-water emulsion were evaluated in rabbits and in beagle dogs.[76] Ciclosporin ophthalmic formulations at concentrations up to 0.4% did not produce any systemic toxicity when administered as often as six times daily for up to 6 months in rabbits and for up to 1 year in dogs. There were no ciclosporin-related histological changes in any organs or tissues. After administration of a 0.4% ciclosporin ophthalmic formulation, mean steady-state C_{max} values of blood ciclosporin were 1.36 μg/L and 0.65 μg/L in rabbits and dogs, respectively. For comparison, oral administration to animals yielded plasma concentrations of ciclosporin ranging from 200 to 5000 μg/L (see section 4.2.2), approximately 200–5000 times the plasma ciclosporin concentrations after topical administration. Thus, systemic ciclosporin concentrations in rabbits and dogs after ocular administration of ophthalmic ciclosporin formulations are minimal in comparison with those after oral administration.

5.2 Humans

The extent of systemic ciclosporin exposure in humans after topical administration was evaluated in clinical studies in which patients received either 0.5% or 2% ciclosporin, in castor, olive or peanut oil (table III).[59,62,64,65] Ciclosporin could be detected in patients' blood in only one[62] clinical study, and in that study the concentration was very low (4.7 μg/L).

Two clinical studies were conducted to evaluate the safety and systemic drug exposure of the ciclosporin castor oil-water emulsion formulation.[57,87] In these studies, the most common adverse event was ocular burning, and no serious adverse events were considered to be related to ciclosporin.

In the first clinical study, 162 dry-eye patients received placebo or ophthalmic 0.05%, 0.1%, 0.2% or 0.4% ciclosporin emulsion twice daily for 12 weeks.[57] Blood samples taken after 1, 4 and 12 weeks of treatment revealed that mean blood ciclosporin concentrations were below the LLOQ

Table IV. Summary of clinical studies of oral administration of ciclosporin

Diagnosis	No. of pts	Dosage (mg/kg/day)	Duration	Adverse events	Results	Reference
Randomised, double-blind trials						
Endogenous uveitis	56	10 initially, then maximum 15	1y	None requiring d/c, but serum creatinine elevations and hypertension were noted	Compared ciclosporin with prednisolone. VA improved in 13/28 pts in each group. Macular oedema resolved in 7/15 ciclosporin pts and 10/16 prednisolone pts (p = 0.376)	3
Chronic idiopathic uveitis	27	10 (with downward taper) or placebo. Both + prednisone 0.3 mg/kg/day	1y	Many reported, but none requiring d/c	Ciclosporin + prednisone better than prednisone alone, but difference not statistically significant. Ciclosporin group fared better at higher dosages, but groups did not differ significantly at lower dosages	81
Behçet's disease	96	10 initially with taper to 6–8 for maintenance Alternate arm: colchicine, 1 mg/day	16wk for initial phase then 44 ± 21wk for maintenance	One d/c with ciclosporin (nephrotoxicity) and two d/c with colchicine (hepatotoxicity). More events reported with ciclosporin	91% of 47 ciclosporin pts vs 33% of 49 colchicine pts improved	6
Uncontrolled, prospective trials						
Uveitis	70	5	Mean 31mo with follow-up up to 8y	Impaired renal function tests in 31.4% of pts 45 pts had >50% increase in hepatic transaminases	46/50 pts responded for up to 3y	82
Ocular inflammation (variable aetiologies)[a]	74	5 initially with a maximum of 7	≥3mo	None requiring d/c, although standard events noted	Over 2y, 52% of pts had improved VA by 1 Snellen line, 33% remained stable, and 19% worsened	83
Behçet's disease	14	5 initially with downward taper to 2	30–38mo	No d/c; some dose reductions required	86% of pts responded positively: 43% had complete disappearance of their ocular attacks and 43% had decreased ocular attacks. Only one pt had decreased VA	64

Continued next page

Table IV. Contd

Diagnosis	No. of pts	Dosage (mg/kg/day)	Duration	Adverse events	Results	Reference
Chronic intraocular inflammation	13	5 initially with downward taper ± prednisolone 15 mg/day	Mean 26mo (range 8–44); mean follow-up 29mo (range 8–49); 1y before dose reduction begins	One pt converted to azathioprine after control was achieved because of nephrotoxicity Four pts developed systemic hypertension, but resolved	VA improved in ten pts and stabilised in three. Improvement was maintained in the majority of pts	84
Chronic posterior uveitis	9	10 in four pts, 5 in five pts with downward taper ± prednisolone 15 mg/day; mean maintenance dose 4 ± 1.1	Mean 17mo (range 6–30)	Some serious AEs, but only one temporary d/c due to serum creatinine elevation	7/9 pts had sustained improvement VA improved in 11 eyes, remained stable in one eye, and worsened in three eyes Three eyes were excluded from study	85
Behçet's disease	21	10 initially in 16 pts and 5 in five pts; titration down to C_{min} of 100–150 μg/L	5–44mo (median 17.6 ± 10.7)	No d/c, although minor creatinine elevations (nine pts) and hypertension (seven mild, four moderate, one severe but controlled) were noted	Decreased intraocular inflammation in all pts. VA improved in 23 eyes, stabilised in 11 eyes, and worsened in eight eyes	7
Behçet's uveitis	12	10, tapered after 1y by 50 mg/mo	Mean 10.8mo (range 3–18)	Three d/c due to nausea and malaise, one d/c due to gingivitis, three dosage reductions due to nephrotoxicity	10/12 pts showed initial improvement, which was maintained in seven pts while on full-dose ciclosporin	8
Uveitis	52	8–10 initially with up to 16, then tapered to reach serum creatinine level of 2 × normal	≤1y	Five pts dropped out before 3mo for undisclosed reasons	41/52 pts improved with ciclosporin. 25/35 remained on ciclosporin at 1y, with 22 retaining an improvement of ≥2 Snellen lines and decrease in vitreal haze by two grading levels. 17/35 were successful on ciclosporin alone without corticosteroids	86

a This study combined both prospective and retrospective data.

AE = adverse event; **C_{min}** = minimum concentration; **d/c** = discontinuation(s); **pt(s)** = patient(s); **VA** = visual acuity.

(0.1 μg/L) in all samples from the 0.05% and 0.1% treatment groups at all sampling times. The highest blood ciclosporin concentration measured in any patient from the 0.05% and 0.1% treatment groups was 0.102 μg/L. The highest blood ciclosporin concentration measured in any treatment group was 0.158 μg/L, from a patient who received 0.4% ciclosporin emulsion.[57]

The second clinical study involved ophthalmic treatment of dry-eye patients with the same ciclosporin concentrations in the same vehicle.[87] Predose blood samples were collected after 1 month of treatment from 113 dry-eye patients, after 6 months of treatment from 94 patients, and from 82 patients after 6–12 months of treatment. Serial blood samples were also taken during one 12-hour dosing interval from 26 patients after 9–12 months of treatment, to characterise blood ciclosporin concentration fluctuations within a single dosing interval at steady state and to quantitate C_{max}. Out of 224 trough blood samples collected and 208 serial blood samples, only ten contained quantifiable ciclosporin (LLOQ 0.1 μg/L). All ten samples were from the 0.1% ciclosporin treatment group; the highest value was 0.299 μg/L. No quantifiable ciclosporin was detected in the blood of any patient receiving ophthalmic 0.05% ciclosporin emulsion in both eyes twice daily for up to 1 year.[87]

One drop of 0.05% ciclosporin emulsion in both eyes twice daily results in a total daily exposure of 0.057mg. By contrast, the daily oral ciclosporin dose for treatment of severe psoriasis recommended by the package insert of Neoral® (Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) [2.5 mg/kg/day or about 190mg total for a 76kg patient][73] is 3000-fold greater. These doses result in mean steady-state blood C_{max} and trough values of ciclosporin of 655 and 74.9 μg/L, respectively.[73] Similar amounts of ciclosporin, 2–3 mg/kg/day or 150–230 mg/day for a 76kg patient, are employed for systemic maintenance administration to treat intraocular inflammatory conditions such as uveitis.[4] Ciclosporin administration for transplant patients receiving systemic immunosuppressive therapy is designed to achieve trough blood ciclosporin concentrations of 20–100 μg/L. Consistent with the fact that daily topical doses are several thousand times less than daily oral doses, blood ciclosporin concentrations in humans after ocular instillation of ciclosporin emulsion (ranging from 0.10 to 0.299 μg/L) are orders of magnitude less than after oral administration.

5.3 Implications for Adverse Effects

Systemic exposure to ciclosporin after ocular administration of the ciclosporin castor oil-water ophthalmic formulation is minimal in humans, rabbits and dogs (sections 5.1 and 5.2). Therefore, the risk of nephrotoxicity and hypertension (hallmarks of systemic adverse effects associated with systemic ciclosporin treatment) is minimal for ophthalmic ciclosporin administration. The ocular safety of ciclosporin ophthalmic formulations has also been documented in human, rabbit and dog studies, obviating concerns about ciclosporin-related ocular infections.

6. Conclusion

Twice-daily instillation of 0.05% ciclosporin castor oil-water emulsion effectively delivers ciclosporin to surface ocular tissues at concentrations sufficient for immunomodulation. By contrast, topically administered ciclosporin penetrates intraocular tissues poorly, and twice-daily instillation of 0.05% ciclosporin emulsion results in plasma ciclosporin concentrations <0.1 μg/L, orders of magnitude below those found during systemic immunosuppressive therapies. In accordance with the low ciclosporin concentrations found in blood and in tissues other than those at the ocular surface, no systemic adverse effects were associated with topical ophthalmic ciclosporin treatment; nor were there any ocular adverse effects except for some mild, transient ocular discomfort. Because of its favourable safety profile and effective delivery of ciclosporin to affected target tissues, the 0.05% ciclosporin castor oil-water formulation appears to be a promising treatment for dry-eye disease.

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