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Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease.

Small DS[1], Acheampong A, Reis B, Stern K, Stewart W, Berdy G, Epstein R, Foerster R, Forstot L, Tang-Liu DD.

Author information

- [1]Allergan, Inc Irvine, CA 92715, USA.

Abstract

To quantify blood cyclosporin A (CsA) concentrations during treatment with CsA topical ophthalmic emulsions, blood was collected from 128 patients enrolled in a Phase 3, multicenter, double-masked, randomized, parallel-group study of CsA eyedrops for treatment of moderate to severe dry eye disease. Patients received 0.05% CsA, 0.1% CsA, or vehicle b.i.d. for 6 months; vehicle-treated patients then crossed over to 0.1% CsA b.i.d. for 6 months. CsA concentrations were measured using a validated LC/MS-MS assay (quantitation limit = 0.1 ng/mL). No patient receiving 0.05% CsA had any quantifiable CsA in the blood (n = 96 samples). All but 7 of 128 (5.5%) trough blood samples from the 0.1% CsA group were below the quantitation limit for CsA; none exceeded 0.3 ng/mL. CsA was also below the limit of quantitation in 205 of 208 (98.6%) of serial postdose blood samples collected from 26 patients during 1 dosing interval between months 9 and 12. The highest C(max) measured, 0.105 ng/mL at 3 hours postdose, occurred in a 0.1% CsA-treated patient. These results indicate that long-term use of topical CsA ophthalmic emulsions at doses that are clinically efficacious for treating dry eye will not cause any system-wide effects.

Ophthalmology. 2005 Oct;112(10):1790-4.

Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years.

Barber LD[1], Pflugfelder SC, Tauber J, Foulks GN.

Author information

- [1]Department of Ophthalmology, University of Arkansas, Little Rock, Arkansas 72205, USA.

Abstract

OBJECTIVE:

To evaluate cyclosporine 0.1% ophthalmic emulsion over a 1- to 3-year period in moderate to severe dry eye disease patients.

DESIGN:

Nonrandomized, multicenter, open-label clinical trial extending 2 ophthalmic cyclosporine phase III clinical trials.

PARTICIPANTS:

Four hundred twelve patients previously dosed for 6 to 12 months with cyclosporine 0.05% or 0.1% in prior phase III trials.

INTERVENTION:

Patients instilled ophthalmic cyclosporine 0.1% twice daily into both eyes for up to 3 consecutive 12-month extension periods.

MAIN OUTCOME MEASURES:

Corneal staining, Schirmer tests, and symptom severity assessments were conducted during the first 12-month extension, with a patient survey during the second 12-month extension. Biomicroscopy and visual acuity (VA) examinations, intraocular pressure (IOP) measurements, and adverse effects queries occurred at 6-month intervals.

RESULTS:

Mean duration of treatment was 19.8 months. Improvements in objective and subjective measures of dry eye disease were modest, probably because of prior treatment with cyclosporine. Most survey respondents said their symptoms began to resolve in the first 3 months of cyclosporine treatment during the previous phase III clinical trials. At study exit, VA decreased in 12.6% (93/738) and increased in 5.4% (40/738) of eyes by > or =2 lines; severity of biomicroscopy findings increased in 3.4% (chemosis; 26/760), 7.2% (conjunctival hyperemia; 55/760), or 8.5% (tear film debris; 64/756) of eyes; and mean IOP increased 0.18 mmHg relative to baseline. The most common treatment-related adverse events were burning (10.9% of patients [45/412]), stinging (3.9% [16/412]), and conjunctival hyperemia (3.4% [14/412]). No serious treatment-related adverse events occurred. Most patients (95.2% [140/147]) said they would continue cyclosporine therapy; 97.9% (143/146) would recommend it to other dry eye patients.

CONCLUSIONS:

Therapy of chronic dry eye disease with cyclosporine 0.1% ophthalmic emulsion for 1 to 3 years was

safe, well tolerated, and not associated with systemic side effects. The results supplement the safety record of the commercially available cyclosporine 0.05% ophthalmic emulsion.