Topical Treatment of Post-Cataract HSV Epithelial Keratitis

To watch a video of this case, visit Eyetube.net and enter the keyword "Zirgan" in the search bar.

BY DEREK CUNNINGHAM, OD

Eye care professionals use topical antiviral medications frequently in patients, and ZIRGAN (ganciclovir ophthalmic gel) 0.15% (Bausch & Lomb, Rochester, NY) is approved by the FDA to treat acute herpetic keratitis (dendritic ulcers). This article describes my recent use of ZIRGAN to treat a large dendritic ulcer.

IMPORTANT RISK INFORMATION

ZIRGAN is indicated for topical ophthalmic use only. Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

Please see complete information about ZIRGAN in the accompanying prescribing information on the next page.

CASE STUDY

A 68-year-old female presented approximately 2 months after cataract surgery complaining of reduced vision. The surgery itself was relatively uneventful, but when I saw her 2 months later, I learned that she had called my staff and reported reduced vision and discomfort for several days after the surgery.

The patient presented with a large dendritic ulcer (Figure 1A). At the time, she was self-medicating with prednisolone acetate and ketorolac tromethamine that remained from the cataract surgery. By using these medications, she was self-inducing immunosuppression that contributed to the size of the dendrite.

In a case like this, I would traditionally institute oral therapy in addition to topical treatments. Due to the severity of the lesion, the risk of vision loss was significant. When treating a lesion of this size and involving this amount of tissue, it is important to preserve as many healthy epithelial cells as possible. ZIRGAN has two mechanisms of action, and it is able to target infected cells as opposed to healthy cells.

MECHANISM OF ACTION

When the active molecule of ZIRGAN, ganciclovir, is activated, it inhibits the synthesis of viral DNA in two ways: competitive inhibition and chain termination. In competitive inhibition, ganciclovir directly inhibits viral DNA polymerase and prevents viral replication. In chain termination, the activated ganciclovir incorporates into viral DNA and prevents DNA synthesis.

TREATMENT AND OUTCOME

I chose to start the patient on ZIRGAN at five times per day, and I asked her to return for daily follow-up visits. Roughly 3 days later, the eye showed complete re-epithelialization (Figure 1B). At that point, I lowered the dosage of ZIRGAN to three times per day for 7 days. On the seventh day, the patient was able to discontinue the medication.

With the dendritic ulcer, The eye's visual acuity was 20/400 (down from 20/25 after the cataract surgery), which was a deep concern for me. I watched this patient on a daily basis, and roughly 10 days after the initial presentation, her UCVA had returned to 20/30. I felt confident that the eye would recover fully. ■

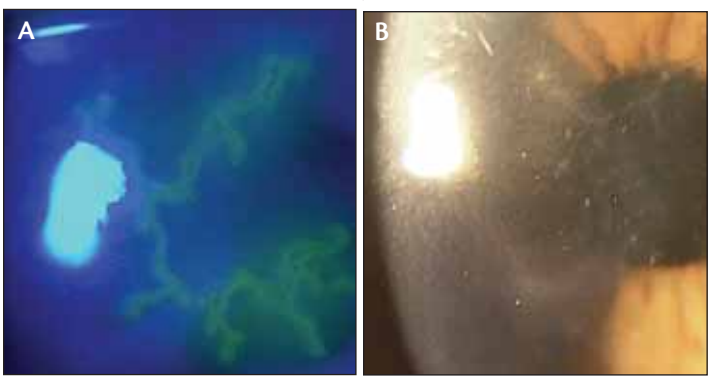

Figure 1. A dendritic ulcer that presented after cataract surgery (A) showed complete re-epithelialization after 3 days of treatment with ZIRGAN gel 0.15% (B). Individual results may vary. In pooled data from three randomized, single-masked, controlled, multicenter clinical trials, resolution (healed ulcers) was achieved at day 7 in 72% of subjects (41 of 57). In one open-label, phase 3, randomized, controlled, multicenter trial, 77% of patients (55 of 71) with dendritic ulcers healed by day 7.

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Zirgan®

ganciclovir ophthalmic gel 0.15%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use ZIRGAN® safely and effectively. See full prescribing information for ZIRGAN.

ZIRGAN (ganciclovir ophthalmic gel) 0.15%

Initial U.S. approval: 1989

----------INDICATIONS AND USAGE----------

ZIRGAN is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers). (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days. (2)

----------DOSAGE FORMS AND STRENGTHS----------

ZIRGAN contains 0.15% of ganciclovir in a sterile preserved topical ophthalmic gel. (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- ZIRGAN is indicated for topical ophthalmic use only. (5.1)
- Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: June 2010

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZIRGAN (ganciclovir ophthalmic gel) 0.15% is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

2 DOSAGE AND ADMINISTRATION

The recommended dosing regimen for ZIRGAN is 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.

3 DOSAGE FORMS AND STRENGTHS

ZIRGAN contains 0.15% of ganciclovir in a sterile preserved topical ophthalmic gel.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

ZIRGAN is indicated for topical ophthalmic use only.

5.2 Avoidance of Contact Lenses

Patients should not wear contact lenses if they have signs or symptoms of herpetic keratitis or during the course of therapy with ZIRGAN.

6 ADVERSE REACTIONS

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Teratogenic Effects

Pregnancy Category C: Ganciclovir has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (approximately 10,000x and 17,000x the human ocular dose of 6.25 mcg/kg/day), respectively, assuming complete absorption. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality. Daily intravenous doses of 90 mg/kg/day (14,000x the human ocular dose) administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

There are no adequate and well-controlled studies in pregnant women. ZIRGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic ganciclovir administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Caution should be exercised when ZIRGAN is administered to nursing mothers.

8.4 Pediatric Use

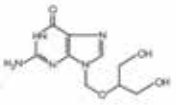
Safety and efficacy in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

ZIRGAN (ganciclovir ophthalmic gel) 0.15% contains a sterile, topical antiviral for ophthalmic use. The chemical name is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (CAS number 82410-32-0). Ganciclovir is represented by the following structural formula:



Ganciclovir has a molecular weight of 255.23, and the empirical formula is $C_9H_{13}N_5O_4$.

Each gram of gel contains: ACTIVE: ganciclovir 1.5 mg (0.15%). INACTIVES: carbopol, water for injection, sodium hydroxide (to adjust the pH to 7.4), mannitol. PRESERVATIVE: benzalkonium chloride 0.075 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZIRGAN (ganciclovir ophthalmic gel) 0.15% contains the active ingredient, ganciclovir, which is a guanosine derivative that, upon phosphorylation, inhibits DNA replication by herpes simplex viruses (HSV). Ganciclovir is transformed by viral and cellular thymidine kinases (TK) to ganciclovir triphosphate, which works as an antiviral agent by inhibiting the synthesis of viral DNA in 2 ways: competitive inhibition of viral DNA-polymerase and direct incorporation into viral primer strand DNA, resulting in DNA chain termination and prevention of replication.

12.3 Pharmacokinetics

The estimated maximum daily dose of ganciclovir administered as 1 drop, 5 times per day is 0.375 mg. Compared to maintenance doses of systemically administered ganciclovir of 900 mg (oral valganciclovir) and 5 mg/kg (IV ganciclovir), the ophthalmically administered daily dose is approximately 0.04% and 0.1% of the oral dose and IV doses, respectively, thus minimal systemic exposure is expected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1,000 mg/kg/day (approximately 3,000x and 160,000x the human ocular dose of 6.25 mcg/kg/day, assuming complete absorption). At the dose of 1,000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (160x the human ocular dose). Except for histocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50 to 500 and 250 to 2,000 mcg/mL, respectively.

In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV) (24,000x to 80,000x human ocular dose) but not 50 mg/kg (8,000x human ocular dose). Ganciclovir was not mutagenic in the Ames Salmonella assay at concentrations of 500 to 5,000 mcg/mL.

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following intravenous doses of 90 mg/kg/day (approximately 14,000x the human ocular dose of 6.25 mcg/kg/day). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 0.2 to 10 mg/kg (30x to 1,600x the human ocular dose).

14 CLINICAL STUDIES

In one open-label, randomized, controlled, multicenter clinical trial which enrolled 164 patients with herpetic keratitis, ZIRGAN was non-inferior to acyclovir ophthalmic ointment, 3% in patients with dendritic ulcers. Clinical resolution (healed ulcers) at Day 7 was achieved in 77% (55/71) for ZIRGAN versus 72% (48/67) for acyclovir 3% (difference 5.8%, 95% CI - 9.6%-18.3%). In three randomized, single-masked, controlled, multicenter clinical trials which enrolled 213 total patients, ZIRGAN was non-inferior to acyclovir ophthalmic ointment 3% in patients with dendritic ulcers. Clinical resolution at Day 7 was achieved in 72% (41/57) for ZIRGAN versus 69% (34/49) for acyclovir (difference 2.5%, 95% CI - 15.6%-20.9%).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIRGAN is supplied as 5 grams of a sterile, preserved, clear, colorless, topical ophthalmic gel containing 0.15% of ganciclovir in a polycoated aluminum tube with a white polyethylene tip and cap and protective band (NDC 24208-535-35).

Storage

Store at 15°C-25°C (59°F-77°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel. If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician. Patients should be advised not to wear contact lenses when using ZIRGAN.

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