Fighting the Battle
Against Herpetic Keratitis

Herpetic keratitis is hardly a common infection, yet it's the leading cause of infectious corneal blindness in America.[1] I have a referral practice for ocular infections, so I see the disease fairly frequently — new, acute cases once per month, established cases with acute flare-ups once a week, and follow-up visits for cases in remission multiple times per week. However, the comprehensive ophthalmologist or optometrist may see only a few cases per year.

It's a challenging disease because it can be sight-threatening and it behaves unpredictably. It's not easy to know when and where flare-ups will occur. In most cases, patients seek help early for outbreaks, which is especially important when the lesion is centrally located and portends significant vision loss if untreated (Figure 1). Once the patient is under our care, antiviral drugs provide a first-line defense.

Acute Axial Herpetic Keratitis

In a typical case of acute para-axial keratitis, a patient goes to the emergency department with a painful red eye. The emergency department doctor thinks that since the patient's vision is OK, the diagnosis must be bacterial conjunctivitis, and it's best to prescribe erythromycin ointment and advise the patient to make an appointment with an eye care provider.

One to 5 days later, the concerned patient comes into our office in the same condition. The exam shows a fine haziness that is localized to one region of the cornea. In addition to the dendritic defect in the epithelium, axial stromal haze is present, and vision is worse. Peripheral vision has clouded, and central vision has dropped 1 or 2 lines to 20/50 to 20/80, even if the keratitis is superficial.

In my experience, roughly half of the cases that are like this one also have an inflammatory response beyond the epithelium, which is especially likely after a delay in treatment.

A key to battling the infection is to treat it with a potent and specific preserved topical antiviral.

An Antiviral Option

While there are other topical antiviral treatment options from which to select, ZIRGAN® (ganciclovir ophthalmic gel) 0.15% is a good choice for the treatment of acute herpetic keratitis (dendritic ulcers). One drop of ZIRGAN® can be instilled in the affected eye 5 times per day (approximately every 3 hours when awake) until the corneal ulcer heals, and then 1 drop 3 times per day for 7 days.[2] The drops are preserved with BAK, a non-mercurial preservative. This antiviral has been proven effective and specific to virus-infected cells.[2] In 3 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.[2] Clinical resolution (healed ulcers) at day 7 was achieved in 72% (41/57) for ZIRGAN® vs 69% (34/49) for acyclovir (difference 2.5%, 95% CI -15.6% to 20.9%).[2]

Recommendations for Managing Herpetic Keratitis Patients[3]

- If significant inflammation is present, treat it with a corticosteroid after the virus is eradicated.
- Use oral antivirals for deeper infections and herpetic uveitis.
- Prompt treatment of recurrences is important; common symptoms of herpetic keratitis are photophobia, pain, redness, and a clear discharge.
- Help patients avoid outbreaks by educating them about triggers such as fever, psychological stress, trauma, and local or systemic medications.

Indication

- ZIRGAN® (ganciclovir ophthalmic gel) 0.15% is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

Important Risk Information about ZIRGAN®

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

Please see prescribing information about ZIRGAN® after this article.

Ganciclovir: my first-line defense for herpetic keratitis

BY JOHN D. SHEPPARD, MD, MMSc

The stereotypical patient is often initially presumed to have a bacterial infection that is eventually identified as a dendritic ulcer instead, and therefore I switch them from erythromycin ointment to ZIRGAN® (ganciclovir ophthalmic gel) 0.15%. For such patients, I prescribe ZIRGAN®, 1 drop in the affected eye 5 times per day (approximately every 3 hours while awake) until the corneal ulcer has healed.[2] We'll then reduce the ganciclovir dosage to 3 times per day for an additional 7 days.[2]

Although this case is typical, every patient is different. In cases where the infection has become very advanced before we see the patient and significant inflammation is present, it may be necessary to use a steroid to reduce inflammation after the virus is eradicated. If the lesions are central — and therefore more sight-threatening we treat the lesions more aggressively.

Ensuring Rx Is Dispensed as Written

In today's world, cost is a factor for patients, so doctors must consider this when determining which medication to prescribe. The perception of high cost and limited managed care access often present a barrier to prescribing ZIRGAN®. Current programs are in place to help offset co-pay costs for patients and this should help ensure patients receive the treatment we prescribe.

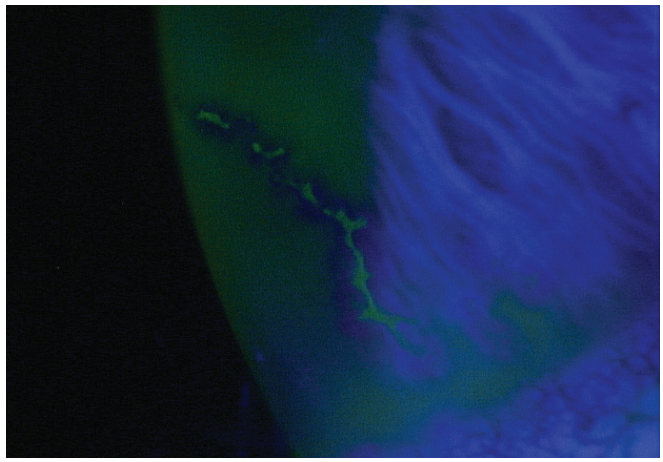

Figure 1. Note classic herpes dendrite across the inferior cornea.

There is no generic equivalent for ZIRGAN®. I've found it beneficial to write, "Dispense as Written (DAW)" on ZIRGAN® prescriptions to help ensure patients get what I prescribe.

With regard to cost, coupons now play a role in many practices. There's an automatic discount program in place for ZIRGAN® to help bring co-pays to a more manageable level.

We achieve excellent results in treating dendritic ulcers with this specific, non-mercurially preserved antiviral agent. To ensure patients receive the treatment we prescribe, educate them on the features of the treatment you choose and tell them not to accept a substitute at the pharmacy.

Indication

- ZIRGAN® (ganciclovir ophthalmic gel) 0.15% is a topical ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis (dendritic ulcers).

Important Risk Information about ZIRGAN®

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

Please see prescribing information about ZIRGAN® after this article.

References

1. National Eye Institute Website. Facts about the cornea and corneal disease. https://nei.nih.gov/health/cornealdisease. Accessed August 12, 2015.
2. ZIRGAN [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2014.
3. White ML, Chodosh J. Herpes simplex virus keratitis: a treatment guideline—2014. ONE® Network Website. http://one.aao.org/clinical-statement/herpes-simplex-virus-keratitis-treatment-guideline. Accessed October 14, 2015.

John D. Sheppard, MD, MMSc, is President of Virginia Eye Consultants in Norfolk, VA. In addition, at Eastern Virginia Medical School, Dr. Sheppard is Professor of Ophthalmology, Microbiology & Molecular Biology Ophthalmology Residency Research Program Director, and Clinical Director of Thomas R. Lee Center for Ocular Pharmacology.

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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: April 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

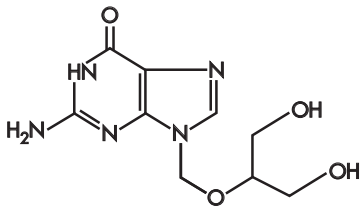
Safety and efficacy in pediatric patients below the age of 2 years have not been established.

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: Carbomer Homopolymer, 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 Fertilty

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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