A Prospective, Double-masked, Placebo Controlled Comparison of Topical 0.15% Ganciclovir Gel (Zirgan®) Versus 0.3% Hypromellose Gel (Genteal Gel®; Placebo) for the Treatment of Herpes Zoster Keratitis While on Oral Anti-viral Treatment

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I. Introduction

Herpes zoster ophthalmicus (HZO) is specific form of herpes zoster, which manifests as an ocular disease. This occurs as a unilateral painful skin rash in a dermatomal distribution of the trigeminal nerve shared by the eye and ocular adnexa. HZO occurs typically in older adults but can present at any age and occurs after reactivation of latent varicella-zoster virus (VZV) present within the sensory spinal or cerebral ganglia.[1]

It is estimated that the lifetime risk of developing a herpes zoster (HZ) viral infection is 10% to 20%.[2] The reactivation of the VZV originates from the sensory ganglia. When the infection involves the first division of the trigeminal nerve (ophthalmic division or V1), this disorder is termed herpes zoster ophthalmicus (HZO). The first division of the trigeminal nerve may be involved 20 times more frequently in an HZ infection than the second or third division.[3]

HZO can result in a variety of ophthalmic sequelae, which may be chronic and recurrent in nature and can result in significant ocular and visual morbidity. The post infection complications affect all regions of the eye and adnexa, including the cornea, conjunctiva, and eyelids. Despite advances in therapy, HZO-related complications can be reduced but not eliminated and ocular damage with loss of vision frequently occurs.

Our study will evaluate the efficacy of ganciclovir ophthalmic gel 0.15% in the treatment of herpes zoster keratitis that results from HZO.

A. Background and Significance of Proposed Research

The cornea is involved in approximately 65% of patients who develop HZO. In a study analyzing the corneal complications of HZO in 93 patients, Liesegang found punctate epithelial keratitis in 51%, early pseudodendrites in 51%, anterior stromal infiltrates in 41%, neurotrophic keratitis in 25%, late corneal mucous plaques in 13%, exposure keratitis in 11% and disciform keratitis in 10%. He suggested that initial corneal lesions were likely due to direct damage from the viral infection, whereas the later sequelae were the result of vasculitis, immune reactions to the viral antigens, delayed hypersensitivity reactions, or damage to the nerves and tissue.[4]

Piebanga and Laibson described some of the late corneal disease associated with HZO, including a chronic epithelial keratitis that was characterized by epithelial mucous plaques, which has also been termed mucous plaque keratitis (MPK). The onset was typically months after the initial presentation. Pavan-Langston et al performed polymerase chain reaction studies on an excised corneal button and observed the response of 4 patients to antiviral therapy. They demonstrated successful use of topical trifluridine, vidarabine, and oral acyclovir individually in different cases.[5] The use of newer topical and oral antivirals may improve the general success rate of treatment.

Late-stage stromal keratitis can occur months after the initial onset of the zoster corneal infection.[6] This condition is characterized by deep stromal inflammation, which presents as a typical disciform lesion or asperipheral keratitis. Corneal edema

may be associated with these lesions. If these lesions are not treated with corticosteroids, a chronic inflammation may develop that leads to neovascularization, scarring, and ulceration of the cornea. Later, lipid deposition may occur. Corticosteroids are used to treat the inflammatory component of these disorders.

Neurotrophic keratitis develops due to VZV affecting the sensory nerves and causing hypoesthesia, which leads to the deterioration of corneal epithelium and a punctate keratopathy. If the epithelial breakdown progresses, large corneal epithelial defects occur. Sterile corneal ulcerations occur that may also become secondarily infected. If untreated, the cornea may become opaque, progressively thin, and may eventually perforate.

For the purposes of our study, we define zoster dendrite as a stuck-on rod shaped or branching lesion without terminal bulbs and not a corneal melt, keratouveitis, sclerouveitis, or corneal erosion related to neurotrophic keratitis.

Ganciclovir ophthalmic gel

Ganciclovir ophthalmic gel 0.15% was approved by the Food and Drug Administration (FDA) in September 2009 for the treatment of acute herpetic keratitis (dendritic ulcers). The results of three pooled phase II studies and one phase III trial demonstrated similar cure rates of ganciclovir ophthalmic gel 0.15% compared to acyclovir ophthalmic ointment 3% at day 7. Ganciclovir ophthalmic gel 0.15% demonstrated non-inferiority compared to acyclovir ophthalmic ointment 3%. Of note, acyclovir ophthalmic ointment is not commercially available in the United States and there are no head-to-head clinical trials of ganciclovir ophthalmic gel compared to trifluridine 1% ophthalmic solution for the treatment of acute herpetic keratitis. Ganciclovir ophthalmic gel 0.15%, has not been studied in patients with stromal keratitis.

Previous trials have shown that topical antivirals have been ineffective in the treatment of herpes zoster keratitis. However, there have been a few unpublished reports of use of Zirgan for herpes zoster keratitis (http://www.revoptom.com/content/c/24774/).

Viral plaque reduction assays have been used to test ganciclovir's antiviral activity in vitro, and ganciclovir was found to be a powerful inhibitor of viral replication for HSV1, HSV2, HZV, EBV, CMV, and HHV6 viruses. The GCV 0.15% strength was adopted on the basis of preclinical studies in experimental animal models of herpetic keratitis, preclinical and clinical pharmacokinetic distribution studies, and controlled clinical trials. The gel formulation allows for even distribution of the active drug, prolongs contact with the cornea better than an ointment, and provides greater efficacy at a concentration of 0.15%. The pH (7.45) and osmolarity (300 osmoles) of Ganciclovir gel 0.15% are close to normal physiological values.

In an experimental model of herpetic keratitis in rabbits ganciclovir ointment demonstrated antiviral activity at a concentration of 0.1% with no positive ocular viral samples after 5 times a day treatment at 12 days and at 14 days when applied 3 times a

day.[7] Using this same mode, Castela et al.[8] showed that ganciclovir gel at concentrations of 0.2%, 0.05%, and 0.0125% applied 4 times a day for 12 days, starting on day 3 after infection, effectively treated herpetic keratitis. Ocular isolates showed no positive viral samples on day 12 with GCV 0.2% and 0.05%, and on day 14 with GCV 0.0125%.

Pharmacology/Pharmacokinetics of Ganciclovir

Ganciclovir is activated to ganciclovir triphosphate by viral and cellular thymidine kinases (TK). This active metabolite then inhibits DNA replication by competitive inhibition and direct incorporation into viral DNA resulting in chain termination. It is designed to work selectively by specifically targeting infected cells. Zirgan is a prodrug that is phosphorylated primarily by infected cells. In contrast, the mechanism of action of trifluridine is nonselective and as a result, it is toxic to healthy cells.[9] Also, trifluridine contains the preservative thimerosal, to which many patients have an allergic sensitivity.[10] Zirgan is preserved with benzalkonium chloride (BAK) rather than thimerosal. While BAK has been shown to cause low-grade toxicity to ocular surface cells, this typically occurs only after long-term and/or frequent use of ophthalmic medications.

Ganciclovir has activity against Epstein-Barr virus, cytomegalovirus (CMV), adenovirus, herpes zoster, and herpes simplex virus (HSV) types 1 and 2.[11,12] [13]

Ganciclovir ophthalmic gel has minimal systemic absorption, with the total daily topical dose approximately 0.04% and 0.1% of oral and intravenous ganciclovir doses, respectively.[13] Rapid penetration of ganciclovir has been demonstrated within 5 minutes with topical administration resulting in therapeutic drug levels in ocular tissue, which is imperative for the treatment of herpetic keratitis.[14]

Ganciclovir ophthalmic gel 0.15% is FDA approved for the treatment of acute herpetic keratitis (dendritic ulcers).[13,15] This study looks at the use of ganciclovir gel for the treatment of zoster keratitis. Current available topical antiviral alternatives are trifluridine 1% ophthalmic solution and vidarabine ointment (VIRA-A Ophthalmic Ointment). Our study will provide data regarding the use of ganciclovir ophthalmic gel as an additional tool in the treatment of herpes zoster keratitis which can have potentially blinding sequelae.

Genteal Gel

Genteal gel is a non-prescription eye lubricant gel and is commonly used for treatment of dry eye, irritated eyes. There is no anti-viral agent within genteal gel.

Oral anti-viral

Acyclovir and valacyclovir are the standard treatments used in patients with herpes zoster[17] to prevent long-term complications, including intraocular complications. Acyclovir and valacyclovir have not been studied as single use treatments of herpes zoster dendrites.

II. Hypothesis

We hypothesize that ganciclovir ophthalmic gel 0.15% will be an effective treatment of herpes zoster dendritic keratitis as measured by reduction of the dendritic ulcer by 90% within 2 weeks in at least 50% of subjects receiving ganciclovir while on oral anti-viral therapy compared with 0% of subjects receiving placebo while on oral anti-viral therapy.

III. Study Objectives

The purpose of this study is to evaluate the efficacy (defined as the reduction in ulcer size by 90%) of topical ganciclovir 0.15% in treatment of herpes zoster dendritic keratitis.

The investigators will enroll 33 patients with a diagnosis of HZO with corneal involvement. Their medical records will be reviewed, including their demographic data as well as ophthalmic and medical histories. Subjects will be recruited from the Department of Ophthalmology at Northwestern University (NU), as well as from the qualified practices of physician members of the Chicago Cornea Association and selected cornea practices nationwide.

IV. Study Population

A. Inclusion Criteria

1. Males and Females, age 18 and above who have been diagnosed with a corneal infection caused by the herpes zoster virus
2. Have not been on ganciclovir gel or any other form of topical antiviral therapy for the past month
3. Able and willing to attend subsequent follow-up visits

B. Exclusion Criteria

1. Associated retinitis
2. Patients with a known allergy to hypromellose gel, ganciclovir, acyclovir, or valacyclovir
3. Patients who will require systemic or intra-vitreal ganciclovir therapy
4. Patients who are pregnant or breastfeeding

V. Study Procedures

A. Study Design

This is a prospective, randomized, parallel group study with two arms: subjects receiving oral anti-virals as standard of care therapy while receiving either ganciclovir ophthalmic gel 0.15% (Zirgan) or a placebo ointment (genteal gel). Subjects with corneal dendritic involvement from herpes zoster will be randomized (1:1) to receive ganciclovir ophthalmic gel 0.15% gel or placebo, which will be applied to the affected eye 5 times a day for 7 days, followed by 3 times a day for an additional 7 days. At two weeks, if the zoster dendrite has not healed, rescue therapy can be performed at

the discretion of the treating physician (Zirgan, the study drug, will not be used as a rescue therapy).

Clinical examinations including a dilated fundus examination will be performed at the Screening/Baseline Visit. Subsequent clinical examinations will be performed at study visits 1, 2, and the End of Study/Early Termination Visit, however, fundus examinations are not completed at subsequent examinations. Two sets of slit lamp photographs will be obtained at each visit.

Slit-lamp photographs can be obtained with fluorescein or Rose Bengal staining; however the same staining method should be used throughout the study. Photos will first be taken without fluorescein or Rose Bengal and then taken with fluorescein or Rose Bengal. Time to reduction ulcer size will be recorded as the primary end point and compared among the two groups from the slit lamp photographs. Slit lamp photographs will be reviewed by a qualified physician, who will be masked to the patient information and the study drug received. Intraocular pressure (IOP) measurement will be performed at each study visit and subjects will receive numbing eye drops prior to the IOP.

Both groups will receive the standard 7-day oral therapy of acyclovir (800 mg po five times daily), valacyclovir (800 mg po five times daily), or valacyclovir (1000 mg po three times daily). This oral anti-viral treatment is being given as standard treatment for herpes zoster to prevent long-term complications, including intraocular complications. If the treating physician feels strongly about an altered dosing regimen, this is allowed as long as it is reported. A topical steroid will not be administered unless there is associated inflammation.

	Screening/ Baseline Visit (Week 0)	**Study Visit 1 (Week 1)**	**Study Visit 2 (Week 2)**	**End of Study Visit/Early Termination Visit (Week 3)**
Informed consent	X			
Medical history	X	X	X	X
Dilated fundus examination	X			
Eye exam	X	X	X	X
IOP	X	X	X	X
Slit lamp photos	X	X	X	X
Oral anti-viral dispensed	X			

Study drug dispensed	X			
Diary reviewed		X	X	

The study drug will be sent to the study doctor in a sealed container that should be opened by the patient at home. Patients will be required to fill out a dosing diary. The dosing diary and the remaining drug must be returned to the NU study site from all participating sites.

A Coded Identifier List (CIL) will contain the subject's name, subject's medical record number, subject's date of birth, and the Study ID Number assigned by the study staff. The CIL will be stored on a secure server, be password protected, and will be maintained by authorized study personnel. Once a subject has been given a Study ID Number, all data collected will be identified through this Study ID Number. Each site will maintain their own Coded Identifier List and Northwestern University will not have access to each site's CIL.

B. Study Drug

Ganciclovir ophthalmic gel 0.15%: Sufficient quantity for 15 eyes. The subjects will put the study drug into affected eye(s) 5 times a day while awake for 7 days, followed by 3 times a day while awake for 7 days, or until healing of corneal ulcer. Clinical examinations will be performed at the Screening/Baseline Visit and study visits 1, 2, and the End of Study/Early Termination Visit.

The drug and placebo will be randomized and distributed to the participating centers that will not have access to the drug by Northwestern University study staff. The study drug will be stored and maintained by the Department of Ophthalmology at Northwestern Memorial Hospital located at 259 E. Erie St., Suite 15-20; Chicago, IL 60611.

C. Subject Compliance

In order to obtain reliable safety and efficacy data, it is critical that each subject complies with the dosing schedule specified in this protocol. Each subject will be given a dosing diary to fill out every time they apply the study drug or placebo.
Subjects must also continue with the intake of their systemic medications prescribed.

D. Randomization and Masking

We anticipate enrollment of 33 patients. The study groups will be assigned in a 1:1 ratio, with expected non-completion rate of 10% this will give us 15 patients per treatment group. Neither the patient nor the study doctor or study staff will be able to pick which study group the patient is in or know which study group the patient is in. If subjects have an infection in both eyes, only on eye will be randomized to receive either Zirgan or placebo. The other eye will be given standard of care treatment.

Subjects will be randomized to receive ganciclovir gel (Zirgan®) versus hypromellose gel (Genteal Gel®; Placebo) to be applied topically. A computer algorithm for random number generation will be used to generate the treatment assignments. The study is double-masked and all site investigators, study staff, and subjects will be masked to the group to which subjects are randomized. Masked study doctors at Northwestern University will be reading all slit lamp photos, including those from the other participating sites. The study staff that will be dispensing the study drug and placebo will also be masked.

E. Rescue Therapy

Rescue therapy is defined as any treatment that would have a therapeutic effect on the herpes zoster keratitis. Rescue therapy will be offered if progressive corneal thinning, corneal inflammation, or worsening of the dendritic keratitis occurs. All uses of rescue therapy will be deemed medically necessary by the site investigator.

If rescue therapy is needed after a subject has treatment failure, the site investigator must report the treatment failure and the type of rescue therapy used to the lead site. The lead site study staff can be reached by calling 312-695-0252.

VI. Risks and Benefits

A. Risks

Ganciclovir ophthalmic gel 0.15%

Most common adverse reactions reported in patients were blurred vision (60%), eye irritation (20%), punctate keratitis (5%), and conjunctival hyperemia (5%).[16]

Dilated fundus examination

The dilation medicine will cause some minor stinging after being placed in the eye. The dilation will cause light sensitivity and blurry vision for 4-6 hours.

Slit lamp photography

Bright flashes may cause discomfort to the subject.

Intraocular pressure (IOP) measurement

Numbing eye drops (proparicaine 0.5% ophthalmic solution) will be used prior to taking subject's intraocular pressure. These eye drops may cause redness and stinging. During the measurement, the study doctor will use a machine that touches the surface of the eyes. In rare circumstances, this machine could scratch the subjects' cornea. Such scratches are usually self-heal in less than 24 hours.

The potential harm to the subjects is loss of privacy and confidentiality. Indirect identifiers will be used to link data obtained from different methods. The key will be stored separately from the data and will be destroyed after data collection has been completed.

B. Benefits

Subjects' herpes zoster keratitis may get better as a result of the use of ganciclovir gel. The knowledge gained from this study may benefit future patients with this condition.

VII. Statistical Considerations

A. Sample Size Justification

We will recruit 33 patients in order to account for drop-out or non-completion rate of 10%, providing approximately 15 patients per treatment group.

With 15 patients per group we have sufficient power to test H:p1=p2 vs H1: p1>p2 with type 1 error of 5%, when true values of p1=55% and p2=5%. See below.

Two Independent Proportions (Null Case) Power Analysis
Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1-P2<=0. H1: P1-P2=D1>0. Test Statistic: Fisher's Exact test

Power	Sample Size Grp 1 N1 Beta	Sample Size Grp 2 N2	Prop|H1 Grp 1 or Trtmnt P1	Prop Grp 2 or Control P2	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actual Alpha
0.9978	30	30	0.5500	0.0500	0.0000	0.5000	0.0500	0.0022

B. Statistics

We will use descriptive statistics to present the data in a convenient fashion, including graphics. Success rates in two treatment groups will be compared using Fisher's Exact test. 95% Confidence intervals for rates in each of the treatment groups will also be provided.

VIII. Ethical Considerations

A. Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than the principal investigator and the co-investigators is prohibited. Medical information resulting from a subject's participation in this study may be given to the subject's primary physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the Faro other government regulatory agency auditors, the Northwestern University Institutional Review Board (IRB), and the IRB of Ann & Robert H. Lurie Children's Hospital of Chicago.

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to

others. These restrictions of disclosure will apply equally to all future information supplied that is indicated as confidential.

The data generated by this clinical study are the property of Northwestern University Department of Ophthalmology (the lead site) and Bausch and Lomb (Sponsor) and should not be disclosed without the prior written permission of NU.

B. Human Subjects Protection

A periodic review will be submitted to the IRB at least once per year. The IRB will be notified of completion of the study. After study completion or termination, a final report will be provided to the IRB to close the study. The investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted. Adverse events that are reported to the FDA as IND Safety Reports will be submitted promptly to the IRB per IRB guidelines.

At least once per year, the IRB will review and give written approval in order to continue the study. This trial will be conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

C. Consent

Prior to study entry, all subjects will be required to sign an informed consent form to participate. All subjects will be informed of new information as it comes available during the study.

D. Protocol Amendments

All changes will be submitted to the IRB. Protocol modifications that impact subject safety or the validity of the study will be approved by the IRB before initiation.

E. Record Storage

FDA and Good Clinical Practice guidelines require that an investigator retain subject identification codes, subject files, and source data for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 15 years after the completion or discontinuation of the trial. This will be followed for the study.

F. Use of Information and Publication

The Principal Investigator, sub-investigators may publish the results of this study in conjunction with appropriate scientific and medical personnel.

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