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Current Practice Patterns and Opinions in the Management of Recent Onset or Chronic Herpes Zoster Ophthalmicus of Zoster Eye Disease Study Investigators

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Abstract

Purpose—To determine practices and opinions among study investigators in the Zoster Eye Disease Study (ZEDS) regarding suppressive valacyclovir treatment for recent onset and chronic Herpes Zoster Ophthalmicus (HZO).

Methods—An internet-based survey was distributed to 170 ZEDS study investigators with questions regarding treatment practices for stromal keratitis in HZO, as well as opinions regarding the efficacy of prolonged antiviral prophylaxis.

Results—The response rate was 72.4% (123/170). Topical steroids and oral antivirals were used by the majority of respondents for stromal keratitis in both recent onset (69.1%, 85/123) and chronic HZO (63.4%, 78/123), ($p=0.86$). Duration of treatment was similar in both recent onset and chronic HZO ($p=0.58$) with 50.4% (124/246) of ZEDS investigators using prolonged treatment for stromal keratitis due to recent onset or chronic HZO. The majority of ZEDS respondents believe that oral antivirals are effective during treatment (70.7%, 87/123).

Conclusions—Approximately half of ZEDS investigators treat HZO with prolonged oral antivirals, in addition to topical steroids, and two thirds believe it is effective. Completion of ZEDS is feasible and necessary to determine whether or not these practices are effective. Participation in this study is necessary to obtain evidence to support treatment that many ophthalmologists use and believe is effective.

Keywords

Herpes zoster ophthalmicus; Practice patterns; Zoster Eye Disease Study

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Supplemental digital content (Survey)

INTRODUCTION

Herpes zoster ophthalmicus (HZO) is caused by the localized reactivation of the varicella-zoster virus (VZV) in the ophthalmic division of cranial nerve V. Herpes zoster infections have serious complications including an acute unilateral painful rash, postherpetic neuralgia (a severely debilitating chronic pain syndrome), acute and chronic eye disease, and potentially fatal strokes. Recent studies using polymerase chain reaction (PCR) testing have shown that some complications of HZO, including dendriform epithelial keratitis and iritis, are associated with chronic and/or recurrent active VZV infection.^{1–6} Dendriform lesions respond to topical and systemic antiviral treatment.^{6,7} In addition, corneas removed from HZO patients during transplantation have been found by PCR to have specific VZV genomic DNA sequences up to 51 years after HZO onset.⁸ Furthermore, the Acyclovir Prevention Trial of the Herpetic Eye Disease Study (HEDS) determined that prolonged suppressive antiviral treatment significantly reduced recurrent eye disease caused by Herpes Simplex Virus (HSV), a different herpes virus, and was most beneficial in stromal keratitis, a disease manifestation considered to be immune mediated with the role of active viral infection unknown.⁹ This treatment is now standard care and has improved outcomes in HSV eye disease. Given the evidence that active VZV infection contributes to complications of HZO, and that suppressive antiviral treatment is effective in HSV eye disease which has similarities to HZO, it is important to determine if suppressive antiviral treatment is effective in HZO.

Although corneal specialists routinely manage recurrent and chronic cases of HZO, there is much variability in the use of antivirals. In addition, there is no evidence from a prospective clinical trial regarding the efficacy of prolonged antiviral therapy to reduce chronic and/or recurrent disease. The Zoster Eye Disease Study (ZEDS), funded by the National Eye Institute (NEI) of the National Institutes of Health (NIH), is a randomized controlled clinical trial that seeks to determine whether prolonged suppressive valacyclovir treatment with 1000 mg orally daily for one year reduces complications of HZO, including eye disease and/or postherpetic neuralgia, when compared to placebo. Over 200 investigators/ophthalmologists at 60 participating clinical centers in the USA are participating in ZEDS.

Currently, antiviral treatment for 7–10 days for acute herpes zoster (HZ), including HZO, is supported by randomized control trials and approved by the Food and Drug Administration (FDA), but there are no established or evidence based guidelines for use of suppressive oral antiviral treatment in chronic and/or recurrent HZO.¹⁰ Despite this lack of evidence, many corneal specialists use this treatment. As reported in a previous survey of 100 corneal specialists conducted in 2010 in preparation for ZEDS, approximately 30% of Kera-net listserv respondents used prolonged antiviral treatment.¹¹ A second Kera-net survey done in preparation for this study identified potential study investigators and preferred antiviral treatment.¹² The purpose of the current survey is to determine the baseline practice patterns and opinions of ZEDS investigators at the beginning of study participant enrollment.

METHODS

In order to gain an understanding of the current antiviral treatment being prescribed by the ZEDS trial principal investigators and co-investigators, a Qualtrics internet-based survey (Provo, UT) was distributed to 170 ZEDS study investigators who had completed participating center applications as of November 1, 2017. This survey was opened in December 2017, with reminders sent for 4 weeks, and closed in January 2018. All responses were anonymous. In order to ensure a sufficiently representative response while maintaining the privacy of the decision to participate, individual reminders were sent to non-respondents by a person outside of the ZEDS organization (confidential fielding of the survey with anonymous storage of the responses). This study was approved by the Institutional Review Board at the New York University School of Medicine.

The survey consisted of 15 questions and was divided into 2 sections (See supplemental digital content). The first section provided 2 clinical vignettes to assess current practices regarding antiviral use for treatment of stromal keratitis in recent onset, defined as within 6 months, and chronic HZO. Specifically, respondents were asked about treatment regimens regarding topical steroids and/or oral antivirals, preferred antiviral drug and dosage, duration of antiviral treatment, and to comment on their antiviral protocol.

The second section assessed respondents' opinions regarding whether prolonged suppressive antiviral treatment could prevent or reduce recurrent and/or chronic HZO during and/or after the period of administration. Lastly, general demographic information was gathered, including years in practice, practice setting (community/private vs academic/university vs other), practice location, number of HZO cases treated in the past year, and percentage of cases treated in past year with chronic/recurrent HZO.

Statistical analyses using Fisher's exact test (for categorical variables) and ANOVA test (for continuous variables) were utilized to compare consistency of opinions and practices between related questions, and to compare opinions and treatment practices between subgroups of clinicians, including practice setting, location, specialty, and years of practice. Analyses were conducted in R Language and Environment for Statistical Computing program version 3.3.2 (Vienna, Austria). The results of this survey were also compared with those of the 2010 Kera-net survey.

RESULTS

Demographics

The survey was sent to 170 ZEDS study investigators. The survey response rate was 72.4% (123/170). Of these respondents, 69.9% (86/123) practiced in an academic/university setting, while 26.0% (32/123) practiced in a community or private setting, and 4.1% (5/123) answered that they practiced in other settings (Table 1). This is similar to the demographics of all ZEDS investigators in that 68.8% (117/170) practiced in academic settings, compared to 31.2% (53/170) who were in community or private practices ($p=0.51$, Table 1).

Current Practice Patterns

In our clinical vignette assessing antiviral use for treatment of stromal keratitis in recent onset HZO, the majority of respondents chose to treat with topical steroids and high dose antivirals (45.5%, 56/123) or low dose antivirals (23.6%, 29/123) (Table 2). A minority of respondents chose to treat with topical steroids alone (24.4%, 30/123). These results were similar to practice patterns for treatment of chronic HZO, with the majority of respondents using topical steroids and high dose antivirals (39.0%, 48/123) or low dose antivirals (24.4%, 30/123), ($p=0.86$) (Table 2). Valacyclovir 1000 mg was the preferred antiviral for both recent onset (61.8%, 76/123) and chronic HZO (63.4%, 78/123). Responses for preferred duration of treatment were also similar in recent onset and chronic HZO ($p=0.58$). In recent onset and chronic HZO, 50.4% and 52.8% (62/123 and 65/123) of respondents, respectively, used prolonged antiviral treatment for as long as steroids were employed, for 1 year, or for longer than 1 year. Only 11.4% and 12.2% (14/123 and 15/123) of respondents did not prescribe antivirals for recent onset and chronic HZO, respectively.

Treatment practice patterns did not vary between academic versus community/private practice settings ($p=0.94$) or geographic regions for both recent-onset ($p=0.69$) and chronic HZO ($p=0.47$) (Table 3). However, number of years in practice was associated with significant variation in treatment (Table 3, $p<0.001$). Respondents who used topical steroids were in practice an average of 22 years compared to respondents who used topical steroids and high or low dose antivirals, who were in practice an average of 13 and 16 years, respectively. Self-reported percentage of chronic HZO cases treated in the community (33.7%) and academic settings (32.2%) were similar ($p=0.78$).

In response to an optional open-ended question asking respondents to describe their antiviral protocol, most frequent comments described using initial high dose antivirals followed by a taper to chronic low dose antivirals for both recent-onset and chronic HZO. For recent onset HZO, respondents ($N=20$) chose to prescribe high dose antivirals for 1–2 weeks followed by low dose antivirals for 1 year. For chronic HZO, there was a longer duration of antiviral treatment with respondents ($N=18$) using high dose antivirals until resolution of disease, followed by long-term or indefinite low dose antiviral prophylaxis.

Current Opinions and Attitudes on Prolonged Antiviral Prophylaxis

When questioned whether they believed prolonged antiviral prophylaxis could prevent or reduce recurrent and/or chronic signs of HZO *during* the period of administration, 70.7% (87/123) of respondents said yes, 5.7% (7/123) said no, and 23.6% (29/123) did not know (Table 4). However, when asked whether prolonged suppressive antiviral treatment could prevent or reduce recurrent and/or chronic signs of HZO *after* the period of administration, 21.1% (26/123) said yes, 25.2% (31/123) of respondents said no, and 53.7% (66/123) did not know.

Comparison of Current Survey to 2010 Kera-net Survey

The results of this study were compared to those of our previous study in 2010, in which 100 corneal specialists responded to a survey sent to subscribers of the Cornea Society Kera-net listserv conducted in preparation for the ZEDS trial (Table 4).¹¹ The majority of Kera-net

respondents were community-based ophthalmologists (69.4%, 68/98), in contrast to the current survey of ZEDS investigators, where the majority of respondents practice in an academic/university setting (69.9%, 86/123, $p < 0.001$, Table 1). In our current survey, ZEDS investigators see a higher volume of HZO patients, with 59.0% (72/122) treating 20 or more cases per year compared to the previous survey, in which only 4.8% (4/84) treated 20 or more cases in the past year ($p < 0.001$, Table 4). The demographics of the study population of the two surveys differ significantly, limiting comparisons that can be made between the responses in the two surveys.

DISCUSSION

Overall, the results of this survey demonstrate that a majority (70.7%, 87/123, Table 4) of ZEDS investigators believe that antivirals are efficacious and can reduce complications of HZO during their period of administration. Approximately half of respondents treat recent-onset and chronic HZO with prolonged antivirals in addition to topical steroids. The length of antiviral treatment is significantly longer ($p=0.008$) among ZEDS investigators who responded to this survey compared to Kera-net subscribers who responded to the 2010 survey (Table 4). The demographics of ZEDS investigators are different from those of the Kera-net listerv, where a majority of respondents were community or private-practice based ophthalmologists who treated a relatively small number of HZO patients. This difference may account for the different practice patterns and attitudes. However, in our current survey there was no significant difference in the treatment practices regarding topical steroid and antiviral use for treatment of stromal keratitis due to HZO between the community and academic settings.

It is unclear why practice patterns and attitudes with regard to antiviral treatment of HZO are different between ZEDS investigators in 2017 and Kera-net respondents in 2010. The demographics of the two study populations vary significantly, so one can not conclude that there has been a shift in practice patterns and attitudes. The current study population of ZEDS investigators may be a self-selected group: they may either already believe that suppressive antiviral treatment is effective, or after being involved in the study, which has been planned since 2010, now believe that it will work. In addition, a recent retrospective study in Italy published in 2014 found that low dose suppressive valacyclovir (500 mg once daily) or acyclovir (400mg twice daily) decreased recurrent episodes of inflammation by 35% in HZO patients (and 39% in HSV patients). This study may have also given some early evidence of the potential efficacy of suppressive antiviral treatment that may have changed some practice patterns.¹³ In addition, another recent publication in 2016 on the epidemiology of recurrent and chronic HZO discussed the importance of studying the role of suppressive antiviral treatment in reducing disease.¹⁴

Despite frequent use of prolonged suppressive antiviral treatment in HZO, it is currently not evidence based. The ZEDS randomized placebo controlled clinical trial of prolonged suppressive valacyclovir treatment is a unique opportunity to obtain evidence to determine standard of care in the treatment of HZO to reduce complications and improve outcomes. We encourage participation in this important clinical trial by enrolling your eligible HZO

patients. Information regarding ZEDS is available on the website <https://med.nyu.edu/research/zoster-eye-disease-study/zoster-eye-disease-study>.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Kido S, Sugita S, Horie S, et al. Association of varicella zoster virus load in the aqueous humor with clinical manifestations of anterior uveitis in herpes zoster ophthalmicus and zoster sine herpette. *Br J Ophthalmol* 2008;92:505–508. [PubMed: 18245272]
2. Van der Lelij A, Ooijman FM, Kijlstra A, et al. Anterior uveitis with sectoral iris atrophy in the absence of keratitis: a distinct clinical entity among herpetic eye diseases. *Ophthalmology* 2000;107:1164–1170. [PubMed: 10857838]
3. Nakashizuka H, Yamazaki Y, Tokumaru M, et al. Varicella-zoster viral antigen identified in iridocyclitis patient. *Jpn J Ophthalmol* 2002;46:70–73. [PubMed: 11853717]
4. Wenkel H, Rummelt C, Rummelt V, et al. Detection of varicella zoster virus DNA and viral antigen in human cornea after herpes zoster ophthalmicus. *Cornea* 1993;12:131–137. [PubMed: 8388787]
5. Pavan-Langston D, Yamamoto S, and Dunkel EC. Delayed herpes zoster pseudodendrites. Polymerase chain reaction detection of viral DNA and a role for antiviral therapy. *Arch Ophthalmol* 1995;113:1381–1385. [PubMed: 7487598]
6. Hu AY, Strauss EC, Holland GN, et al. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. *Am J Ophthalmol* 2010;149:214–220. [PubMed: 19909942]
7. Aggarwal S, Cavalcanti BM, and Pavan-Langston D. Treatment of pseudodendrites in herpes zoster ophthalmicus with topical ganciclovir 0.15% gel. *Cornea* 2014;33:109–113. [PubMed: 24322809]
8. Mietz H, Eis-Hubinger AM, Sundmacher R, et al. Detection of varicella-zoster virus DNA in keratectomy specimens by use of the polymerase chain reaction. *Arch Ophthalmol* 1997;115:590–594. [PubMed: 9152125]
9. Herpetic Eye Disease Study Group. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *N Engl J Med* 1998;339:300–306. [PubMed: 9696640]
10. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology* 2008;115:S3–S12. [PubMed: 18243930]
11. Sy A, McLeod SD, Cohen EJ, et al. Practice patterns and opinions in the management of recurrent or chronic herpes zoster ophthalmicus. *Cornea* 2012;31:786–790. [PubMed: 22269677]
12. Sackel DJ, Castano E, and Cohen EJ. Physician survey for study of suppressive antiviral treatment to reduce chronic ocular disease and postherpetic neuralgia after herpes zoster ophthalmicus. *Eye Contact Lens* 2014;40:200–206. [PubMed: 24892787]
13. Misserochi E, Fogliato G, Bianchi I, et al. Clinical features of ocular herpetic infection in an Italian referral center. *Cornea* 2014;33:565–570. [PubMed: 24763121]
14. Tran KD, Falcone MM, Choi DS, et al. Epidemiology of Herpes Zoster Ophthalmicus: Recurrence and Chronicity. *Ophthalmology* 2016;123:1469–1475. [PubMed: 27067924]

TABLE 1:

Demographics

	Community		Academic		Other	
	<i>n</i>	(%)	<i>n</i>	%	<i>n</i>	%
ZEDS Survey Respondents (n=123)	32	(26.0)	86	(69.9)	5	(4.1)
All ZEDS Investigators (n=170) *	53	(31.2)	117	(68.8)	0	(0.0)
2010 Keranet Respondents (n=98) **	68	(69.4)	29	(29.6)	1	(1.0)

Other (ZEDS survey respondents, n=5): mixed academic university/private: 3, public hospital: 1, private cornea practice: 1

Other (2010 Keranet respondents, n=1): HMO: 1

* P value comparing demographics of ZEDS survey respondents (Row 1) vs all ZEDS investigators (Row 2): p=0.51

** P value comparing demographics of ZEDS survey respondents (Row 1) vs 2010 Keranet survey respondents (Row 3): p<0.001

TABLE 2:

Current treatment practices for recent onset vs. chronic HZO

	Recent Onset HZO		Chronic HZO		<i>p</i> -value
Total respondents, n=123	<i>n</i>	(%)	<i>n</i>	(%)	
Treatment Practice					p=0.86
Topical steroids and high dose antivirals	56	(45.5)	48	(39.0)	
Topical steroids and low dose antivirals	29	(23.6)	30	(24.4)	
Topical steroids	30	(24.4)	32	(26.0)	
Other*	8	(6.5)	13	(10.6)	
Preferred antiviral					p=0.80
Valacyclovir 1000mg	76	(61.8)	78	(63.4)	
Acyclovir 800mg	20	(16.3)	17	(13.8)	
Valacyclovir 500mg	12	(9.8)	9	(7.3)	
Famciclovir 500mg	2	(1.6)	1	(0.8)	
Other	3	(2.4)	1	(0.8)	
No answer (left blank)	10	(8.1)	17	(13.8)	
Duration of treatment					p=0.58
1-2 weeks	32	(26.0)	26	(21.1)	
1 year	19	(15.4)	22	(17.9)	
As long as steroids	35	(28.5)	28	(22.8)	
Longer than 1 year	8	(6.5)	15	(12.2)	
I would not use antivirals	14	(11.4)	15	(12.2)	
Other	9	(7.3)	10	(8.1)	
No answer (left blank)	6	(4.9)	7	(5.7)	

* Other includes antivirals alone (i.e. high dose antivirals, low dose antivirals, or combination of high and low dose antivirals only)

TABLE 3:

Treatment Practice Responses by Demographics

	Topical steroids and high dose antivirals	Topical steroids and low dose antivirals	Topical steroids	p-value
Community				
n (%)	14 (11.4)	9 (7.3)	7 (5.7)	
Academic				
n (%)	41 (33.3)	20 (16.3)	19 (15.4)	p=0.94
Recent Onset HZO				
Mean years in practice $\pm$ SD	12.75 $\pm$ 8.1	15.57 $\pm$ 10.7	22.32 $\pm$ 11.1	p <0.001
Chronic HZO				
Mean years in practice $\pm$ SD	13.11 $\pm$ 9.1	16.33 $\pm$ 10.8	22.03 $\pm$ 10.2	p <0.001
Geographic region n (%)				
Recent Onset HZO				
Northeast	20 (16.3)	9 (7.3)	10 (8.1)	
Southeast	8 (6.5)	5 (4.1)	9 (7.3)	
Midwest	11 (8.9)	4 (3.3)	6 (4.9)	
Southwest	8 (6.5)	6 (4.9)	2 (1.6)	
West	9 (7.3)	5 (4.1)	3 (2.4)	p=0.69
Chronic HZO				
Northeast	14 (11.4)	11 (8.9)	12 (9.8)	
Southeast	7 (5.7)	5 (4.1)	9 (7.3)	
Midwest	12 (9.8)	3 (2.4)	5 (4.1)	
Southwest	9 (7.3)	6 (4.9)	2 (1.6)	
West	6 (4.9)	5 (4.1)	4 (3.3)	p=0.47
	Community	Academic	p-value	
Mean percentage (%) of HZO cases with chronic disease $\pm$ SD	33.7 $\pm$ 27.3	32.2 $\pm$ 25.9	p=0.78	

TABLE 4:

Treatment practice patterns and beliefs in current survey vs 2010 survey

	Current survey		2010 survey		p-value
	<i>n</i>	(%)	<i>n</i>	(%)	
Treatment practice					
Topical steroids	62	(25.2)	24	(24.0)	
Topical steroids and antivirals	163	(66.3)	71	(71.0)	
Other **	21	(8.5)	5	(5.0)	
Total	246 *	(100.0)	100	(100.0)	0.52
Duration of antiviral treatment					
7-10 day course	64	(26.0)	36	(36.7)	
One year or longer	54	(22.0)	15	(15.3)	
As long as steroids are administered	70	(28.5)	16	(16.3)	
I would not use antivirals	28	(11.4)	17	(17.3)	
Other / no answer	30	(12.2)	14	(14.3)	
Total	246 *	(100.0)	98	(100.0)	0.008
Belief in efficacy of prolonged prophylaxis during prophylaxis administration:					
Yes	87	(70.7)	54	(56.3)	
No	7	(5.7)	14	(14.6)	
I do not know	29	(23.6)	28	(29.2)	
Total	123	(100.0)	96	(100.0)	0.02
Belief in efficacy of prolonged prophylaxis after prophylaxis administration:					
Yes	26	(21.1)	27	(27.6)	
No	31	(25.2)	45	(45.9)	
I do not know	66	(53.7)	26	(26.5)	
Total	123	(100.0)	98	(100.0)	0.37
Number of HZO cases treated in the past year:					
<20	50	(41.0)	80	(95.2)	
>20	72	(59.0)	4	(4.8)	
Total	122	(100.0)	84	(100.0)	<0.001

* n=246 is the sum of responses for both recent and chronic onset HZO in the current survey, which was combined to compare to the 2010 survey. There was no statistical difference between responses for recent and chronic HZO in the current survey (p=0.62)

** Other: includes responses where antivirals alone were used