Treatment of herpes zoster ophthalmicus: A systematic review and Canadian cost-comparison

Stacy Fan, BMSc,* Daniel Stojanovic, BHSc,* Monali S. Malvankar-Mehta, PhD,*,† Cindy Hutnik, MD, PhD*,†

ABSTRACT ●

Objective: A systematic review and cost comparison were conducted to determine the optimal treatment of active herpes zoster ophthalmicus (HZO) in immunocompetent adults.

Design: A literature search of MEDLINE, EMBASE, CINAHL, Cochrane Library, BIOSIS Previews and Web of Science, ClinicalTrials.gov, International Clinical Trials Registry Platform, Networked Digital Library of Theses and Dissertations, and Canadian Health Research Collection was performed. The search period was from January 1990 to March 2017.

Participants: Collectively, 516 immunocompetent patients with active HZO treated with oral antivirals were included.

Methods: Randomized controlled trials (RCTs) investigating treatment of active HZO in immunocompetent adults, with one oral acyclovir monotherapy arm, were included. Studies fulfilling inclusion criteria were subjected to quality assessment and data extraction. Provincial drug formularies were consulted to extrapolate cost comparison for investigated treatment regimens.

Results: A total of 1515 titles and abstracts and 9 full-text articles were assessed. Three RCTs met the inclusion criteria. Treatment with oral acyclovir (800 mg 5 times daily for 10 days) was superior to placebo in the prevention of ocular manifestations. Oral famciclovir (500 mg 3 times daily for 7 days) and valacyclovir (1000 mg 3 times daily for 7 days) resulted in comparable rates of ocular manifestations relative to oral acyclovir (800 mg 5 times daily for 7 days). According to provincial drug formulary data, famciclovir and valacyclovir are more affordable across Canada with the recommended dosing schedules.

Conclusions: Oral famciclovir and valacyclovir are reasonable alternatives to oral acyclovir for treatment of active HZO in immunocompetent individuals. Their simpler dosing schedules are associated with a cost benefit that is consistent across Canada.

Herpes zoster (HZ) is a reactivation of latent varicella zoster virus (VZV) within the dorsal root ganglia, which classically presents as a painful vesicular rash along a unilateral dermatomal pattern.[1] In 10%–20% of these cases, reactivation occurs along the ophthalmic division of the trigeminal nerve, resulting in herpes zoster ophthalmicus (HZO).[1,2] Although HZ is classically understood as a self-limiting disease, viral replication within and around the trigeminal nerve may cause ocular complications through direct invasion, vascular and neural inflammation, immune reactions, and tissue scarring.[1,3]

Fifty percent of patients with untreated HZO develop ocular complications.[4] Keratitis is the most common ocular manifestation, followed by iritis, uveitis, conjunctivitis, and scleritis.[4] HZ in any dermatome may result in postherpetic neuralgia, a chronic condition in which pain persists or relapses, possibly years after HZ rash has healed.[5,6] More severe complications of HZO occur when the optic nerve, retina, and central nervous system are involved.[1] The rates of ocular complications secondary to HZO increased 23% between 1970 and 2007.[4] Despite HZO having a self-limiting trajectory, early diagnosis and treatment is indicated because of the potential for vision loss and other disease sequelae.

Management of HZ with antiviral medication reduces the duration and severity of acute zoster manifestation.[7] Currently, the standard treatment is acyclovir, which is both effective and well tolerated.[1,8] Acyclovir is a nucleic acid analogue that functions as a DNA chain terminator, preventing viral replication. Acyclovir is activated specifically by viral thymidine kinases and becomes active only in cells infected by DNA viruses, such as VZV and herpes simplex virus 1 and 2.[9–11] Topical acyclovir is associated with increased ocular complications and more severe pain in comparison to oral acyclovir.[12] When administered within 72 hours of onset of the initial skin lesion, oral acyclovir 800 mg 5 times daily for 7 days reduces the incidence of acute ocular complications, duration of acute pain, and postherpetic neuralgia.[13,14] Because of its versatility, oral acyclovir is frequently administered in HZO management.

The purpose of this study is to establish whether there is any benefit to prescribing alternate antiviral medications to guide the practice of Canadian ophthalmologists treating HZO. This systematic review will investigate whether there are any improvements in outcomes, primarily ocular complications, when comparing oral acyclovir monotherapy with other oral antiviral agents in the treatment of active HZO in immunocompetent adults. A cost

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comparison of validated drug regimens will be extrapolated using provincial drug formularies for the Canadian context.

Methods

Literature search

A literature search of MEDLINE, EMBASE, CINAHL, the Cochrane Library, BIOSIS Previews, and Web of Science was performed (see Appendix 1 for search strategy, available online). Articles were restricted to publication in the English language between January 1990 (the year Dawson's "Herpetic eye disease study"[15] was published) and March 28, 2017. OVID AutoAlerts were set up to send monthly updates with any new literature. Monthly updates were performed on HEED, PubMed, and Cochrane Library databases.

Grey literature was identified by searching the International Clinical Trials Registry Platform, the Networked Digital Library of Theses and Dissertations, Canadian Health Research Collection, and ClinicalTrials.gov. Key words included "herpetic eye disease" and "herpes zoster," combined with "acyclovir." Searches were modified to accommodate the unique terminology and syntax of each database. The resultant list was then screened.

Study selection

Two reviewers (S.F. and D.S.) performed the literature screening independently. A level 1 screening of articles by title and abstract was conducted, followed by a level 2 full-text screening. Discrepancies were settled through discussion, and rationales for decisions were documented.

Selection criteria

Studies were included in the analysis if they (*i*) were published as randomized controlled trials (RCTs) with at least one oral acyclovir monotherapy arm, (*ii*) evaluated patients who were immunocompetent adults (aged ≥18 years) diagnosed with HZO, (*iii*) were published in English, and (*iv*) reported ocular outcomes after treatment with oral antiviral.

Methodological Quality Assessment

The risk of study bias was assessed using the "Quality Assessment Tool for Quantitative Studies" published by *Effective Public Health Practices*.[16] Two reviewers (S.F. and D.S.) completed the assessment tool independently, and discrepancies were resolved with discussion leading to consensus. These data are summarized in Table 1.

Data extraction

The following information was extracted from the selected articles: author, year of publication, study location, study design, total patients enrolled in the study, total patients who completed the study, patient demographic characteristics, treatment groups, dose and schedule of interventions, duration of follow-up, and rates of ocular sequelae.

Treatment effectiveness

Treatment effectiveness was determined based on treatment outcomes reported in included studies. Data on rates of intraocular involvement, development of ocular complications, pain scores and time to resolution, and persistent ocular lesions were obtained for various treatment groups.

Cost comparison

The cost of prescribing the systemic/oral antiviral agents was evaluated by consulting drug benefit formularies for Ontario,[17] Quebec,[18] Manitoba,[19] Saskatchewan,[20] Alberta,[21] British Columbia,[22] Nova Scotia,[23] Newfoundland and Labrador,[24] and Yukon[25] as published by the respective government agencies. Drug benefit formularies were consulted for the remaining provinces and territories in Canada but were excluded because of insufficient information (i.e., did not include dollar value for cost of medication). Dosing regimen was determined by the recommendations made in the included studies. The cost of various treatments was compared, and percentage differences between treatments were obtained.

Results

Search results

Figure 1 presents a PRISMA flowchart of study selection. Our initial search yielded 1515 publications: 519 from Medline, 862 from EMBASE, and 134 from CINAHL. A grey literature search identified 231 clinical trials to be screened: 148 from the International Clinical Trials Registry Platform, 16 from Clinicaltrials.gov, and 67 from Canadian Health Research Collection. A total of 275 duplicate studies were removed. Based on title and abstract screening, we deemed 1462 articles ineligible and retrieved 9 articles for full-text review. Of these, 1 was a duplicate publication of the same trial and institution,[26] 4 did not compare oral monotherapy against oral acyclovir,[13,27–29] and 1 did not report the difference in outcomes on intraocular sequelae between treatment groups and

Table 1—Quality assessment of included studies, based on Quality Assessment Tool for Quantitative Studies by Effective Public Health Practices

Reference	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop Outs	Global Rating
Harding and Porter[31]	Weak	Moderate	Weak	Weak	Moderate	Strong	Weak
Tyring et al.[26]	Strong	Strong	Moderate	Moderate	Moderate	Strong	Strong
Colin et al.[32]	Moderate	Moderate	Moderate	Moderate	Moderate	Strong	Strong

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