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Recurrent herpetic keratitis despite antiviral prophylaxis: A virological and pharmacological study

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ABSTRACT

Recurrent herpes simplex keratitis (HSK) is a leading infectious cause of blindness in industrialized countries. Antiviral prophylaxis (AVP) may fail to prevent recurrence of HSK due to viral resistance, inadequate dosing, or poor patient compliance. In this prospective multicenter study, we enrolled immunocompetent patients with recurrent HSK despite AVP. Ocular samples were tested by PCR for herpes simplex virus 1 (HSV-1). HSV-1 drug resistance was assessed with a genotypic assay based on UL23 and UL30 gene sequencing. After curative full dose valacyclovir (VACV) treatment was started, peak and trough acyclovir (ACV) plasma concentrations were measured, and patient compliance to AVP was assessed with a questionnaire.

The study sample was comprised of 43 patients. Six (14%) patients were positive for HSV-1 using PCR, of whom 5 (83%) harbored genotypically ACV-resistant (ACV^R) virus, due to mutations in UL23 (n = 4) or UL30 (n = 1). Disease duration was statistically significantly longer in patients with viral resistance compared to other HSK patients [35.5 ± 23.4 years (range, 6.8–68.4 years) versus 11.1 ± 12.3 years (range, 0.8–56.3 year) respectively; Mann-Whitney $p = 0.01$)].

While patients were treated with full dose VACV, trough ACV plasma concentrations were below the threshold for ACV sensitivity in 9.5% of cases, and compliance was poor in 5.3% of cases.

To summarize, HSV-1 resistance to ACV seems to be a significant cause of failure of prophylaxis in patients with HSK and is associated with longer disease duration. Most PCR-positive samples contained genotypically ACV^R virus and identification may aid in adapting treatment. Incomplete 24-h drug coverage may also explain some cases of failure of prophylaxis.

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Abbreviations

ACV	Aciclovir
ACV^R	Aciclovir resistant
AVP	Antiviral prophylaxis
AT	Aqueous tap
CMV	Cytomegalovirus
CT	Cycle Threshold
HEDS	Herpetic Eye Disease Study
HSK	Herpes simplex keratitis
HSV-1	Herpes simplex virus 1
Pol	DNA polymerase
TK	Thymidine kinase
SS	Schirmer strip
VACV	Valaciclovir
VZV	Varicella zoster virus

1. Introduction

Herpes simplex keratitis (HSK) is the most common ocular manifestation of herpes, with an incidence ranging from 18.2 to 25.8/100 000 inhabitants per year (Labetoulle et al., 2005; Liesegang, 1989). After the first episode of HSK, recurrent episodes occur in the majority of patients (Liesegang, 1989). Recurrences can lead to visual loss, due to corneal opacification and neovascularization, making HSK one of the leading causes of infection-related blindness in industrialized nations (Farooq and Shukla, 2012).

In the early 2000s, the Herpetic Eye Disease Study (HEDS) demonstrated that long-term antiviral prophylaxis (AVP) with oral acyclovir (ACV) significantly reduced the risk of recurrent HSK (Herpetic Eye Disease Study Group, 1998; Herpetic Eye Disease Study Group, 2000). The outcome of the HEDS study had a major impact on ophthalmic practice worldwide, and health authorities in several countries recommended AVP with oral ACV for 12 months after a recurrent episode of HSK. Since approval, prescriptions of these medications increased significantly worldwide, most often for long-term prophylaxis. Valacyclovir (VACV) is a L-valine esterified prodrug of ACV, with greater oral bioavailability than the parent molecule (MacDougall and Guglielmo, 2004). Based on bioequivalence studies and clinical trials (Miserocchi et al., 2007; Weller et al., 1993), health authorities also recommended VACV for the prevention of recurrent HSK. Most physicians use VACV rather than ACV for practical reasons.

However, AVP fails in a significant number of patients, (Herpetic Eye Disease Study Group, 1998; Herpetic Eye Disease Study Group, 2000), leading some physicians to continue treatment for more than 12 months (Labetoulle and Colin, 2012). As seen in other chronic viral diseases (Wyles, 2013), this long-term antiviral exposure may facilitate the selection of ACV-resistant (ACV^R) Herpes simplex virus 1 (HSV-1) strains strains. Initially reported in immunocompromised patients (Bodaghi et al., 2000), this resistance was subsequently reported in immunocompetent patients, and the proportion of ACV^R isolates has increased in recent years (Duan et al., 2008; van Velzen et al., 2013). Management of patients who experience recurrences despite AVP is challenging, as these recurrences may be due to viral resistance, poor drug absorption, or poor patient compliance to AVP.

This prospective multicenter study investigated these three main potential reasons for clinical resistance to AVP in patients who experienced recurrent HSK despite VACV AVP. It was designed to adhere as closely as possible to routine clinical practice, as the final aim was to determine whether ocular sampling for resistance testing and plasma antiviral drug assay might be of clinical benefit in the real-life setting.

2. Material and methods

This study evaluated the three main potential causes of clinical resistance to AVP including, viral resistance, poor drug absorption, or poor patient compliance to AVP. Acyclovir was assayed in plasma, and viruses detected by PCR in ocular samples were analyzed for genetic resistance to ACV. Patient compliance to AVP was assessed with a questionnaire.

2.1. Study design

This non-interventional, prospective, multicenter study enrolled patients recruited from 12 university hospitals in France from January 2010 to June 2014 (details in the *HEDGOF* list). The protocol was approved by the Ile-de-France VII ethics committee and adhered to tenets of the Declaration of Helsinki. All the subjects gave written informed consent to participate in the study.

2.2. Patients

All patients presenting with presumed or proven recurrent HSK were considered for inclusion. Clinical diagnosis of HSK was based on: i) slit lamp examination for epithelial, stromal or endothelial abnormalities typical of HSV-1 infection; ii) the disease history (multiple relapses, in the same eye, of epithelial, stromal or endothelial keratitis or keratouveitis), including the efficacy of antiherpetic treatment (oral VACV, oral or topical ACV, topical ganciclovir or trifluridine) for previous episodes; and iii) no history of herpes zoster ophthalmicus.

2.3. Inclusion and non-inclusion criteria

The inclusion criteria were: i) an ongoing first or subsequent recurrence of HSK (which refers to the clinical definition given in the preceding paragraph) despite VACV prophylaxis for at least 2 months; ii) age over 18 years; iii) body weight between 40 and 90 kg for females and between 50 and 100 kg for males, iv) written consent to participate in the study, and v) social insurance coverage.

The non-inclusion criteria were: i) a known history of creatinine clearance (CrCl, estimated using the MDRD equation) below 60 mL/min, or hepatocellular failure; ii) ocular surgery in the past 6 months; iii) inclusion in a clinical trial in the preceding 3 months; iv) documented allergy to ACV, VACV and/or their excipients; iv) pregnancy or lactation, v) females of childbearing potential without effective contraception; vi) an ongoing severe or unstable systemic disease, as determined by the investigator recording the patient's medical history (especially any disease or treatment that could affect the glomerular filtration rate or the immune system).

The date of enrollment corresponded to the date of selection, so that ocular sampling could be performed prior to beginning curative treatment (high-dose VACV) for the ongoing HSK relapse.

2.4. Endpoints

The main outcome measure was the proportion of patients with ACV^R HSV-1 strains among all PCR-positive patients. Secondary outcome measures were i) genetic analysis of HSV-1 isolated from tears or aqueous humor (AH), ii) ACV peak and trough plasma concentrations and, iii) patient compliance to VACV AVP, as assessed with a questionnaire.