Use of Antiherpes Drugs and the Risk of Kaposi’s Sarcoma: Data from the Multicenter AIDS Cohort Study

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Kaposi’s sarcoma (KS) is an important cause of morbidity in patients with AIDS, particularly in homosexual men. Epidemiologic features of AIDS-associated KS have led to the hypothesis that it is caused by an infectious cofactor in addition to human immunodeficiency virus (HIV)-1 [1, 2]. Recently, Chang et al. [3] identified unique herpesvirus-like DNA sequences in AIDS-associated KS tissues. Confirmation of this finding in tissues from patients with African endemic KS and classic (Mediterranean) KS [4, 5] has further strengthened the hypothesis that a herpesvirus, provisionally termed Kaposi’s sarcoma-associated herpes virus (KSHV), is the cause of KS.

If such a herpesvirus does cause KS, then use of drugs with activity against herpesviruses might protect against or delay the development of AIDS-associated KS. We tested this hypothesis by analyzing data on the use of acyclovir, ganciclovir, and foscarnet in a longitudinal study of homosexual and bisexual men.

Methods

Study population. The Multicenter AIDS Cohort Study, initiated in 1984, prospectively follows gay and bisexual men semiannually in four metropolitan areas in the United States: Baltimore-Washington, Chicago, Los Angeles, and Pittsburgh; it is described in detail elsewhere [6]. More than 93% of the cohort had known clinical outcomes or were still being followed at the time of this analysis (after 11 years of follow-up). The analyses reported here are limited to the 935 men who developed a clinical AIDS-defining condition [7] after the sixth semianual study visit in 1986, the visit at which data collection on acyclovir use commenced.

Study design. Figure 1 outlines the case-control and longitudinal arms of the study design. The association of self-reported acyclovir use with the occurrence of KS as an initial AIDS diagnosis (hereafter referred to as early KS) was explored in an unmatched, nested case-control analysis. Cases were men with early KS, and controls were those with other initial AIDS diagnoses.

The associations of acyclovir, ganciclovir, and foscarnet use with the occurrence of KS after (non-KS) initial AIDS diagnosis (hereafter referred to as late KS) were explored in a longitudinal analysis. The longitudinal analysis enabled adjustment for differential survival after AIDS onset by treatment group, which might otherwise bias the association between acyclovir use and late KS [8]. Men with early KS were excluded from the analysis of late KS.

The associations between ganciclovir and foscarnet use and KS were explored only in relation to late KS in men with cytomegalovirus (CMV) disease, since these drugs were used almost exclusively to treat CMV.

Study covariates. Beginning with visit 11 (1989), acyclovir use was reported separately when used specifically “to help fight AIDS or HIV” in contrast to use for “health reasons not related to AIDS.” Since use of acyclovir for HIV was less intermittent than use for other indications [8], acyclovir was categorized separately as “use for HIV infection” or “use for any indication” (including HIV infection). Responses to the acyclovir drug questions were available for >95% of person-visits. In the case-control analysis, acyclovir use was defined as self-reported use of acyclovir at any visit before diagnosis of early KS. This definition of
Figure 1. Overview of study design. Association of acyclovir use with the development of KS as initial AIDS diagnosis (early KS) was explored in nested case-control analysis. Associations of acyclovir, ganciclovir, and foscarnet use with development of KS as later manifestation of AIDS were explored in longitudinal analysis.

Acyclovir use does not take into account duration or consistency of dosing. In the longitudinal analysis, use of acyclovir, ganciclovir, and foscarnet were modeled as time-dependent covariates.

A previously derived and validated [9] composite risk score for KS was included as a covariate in the case-control and longitudinal analyses. The score, which has a maximum value of 12, is obtained by the sum of the following weighted baseline characteristics: sexual contact from Los Angeles or San Francisco, 2 points; history of gonorrhea, genital herpes, hepatitis, genital/anal warts, or scabies, 1 point each; poppers used in the 2 years before study entry, 2 points; 0–14, 15–48, or ≥49 male sex partners in the 2 years before study entry, 1, 2, or 3 points, respectively.

Statistical analysis. In the case-control analysis, unconditional multiple logistic regression was used to adjust for potential confounding variables, including race, age, study site, history of genital herpes or herpes zoster, occurrence of genital herpes or herpes zoster before AIDS, sexual practices (e.g., rimming), smoking history, CD4 cell count and hemoglobin concentration within 12 months before AIDS, year of AIDS diagnosis, and individual components of the composite risk score for KS as well as the score itself. Logistic regression with stepwise forward selection of covariates was done using the default criterion for model entry of P < .05 and forcing the acyclovir covariates into the model.

In the longitudinal analysis, Cox proportional hazards models [10] were fitted to time to late KS from a non-KS AIDS diagnosis and time to late KS from first diagnosis of CMV disease. Time-dependent covariates were used for the following variables: CMV disease, zidovudine use, Pneumocystis carinii prophylaxis, acyclovir use, ganciclovir use, foscarnet use, and whether the participant attended the visit after his diagnosis of AIDS. The latter variable addresses a potential bias introduced by the fact that sicker patients, who are more likely to develop KS, may not be well enough to attend the study visit and therefore may not be ascertainment for later use of antiviral drugs. If a participant used zidovudine before a diagnosis of AIDS, this was modeled as a separate covariate, and the time-dependent covariate for zidovudine use after AIDS was automatically set to zero irrespective of later zidovudine use. This was done to account for the time-limited efficacy of zidovudine therapy [11]—that is, those who use zidovudine before AIDS may not benefit significantly with respect to survival after AIDS.

All drug therapy covariates were modeled using the intention-to-treat paradigm for the primary analysis; once a participant reported use of a drug, continued use of the drug was assumed until death or censoring. The intention-to-treat analysis provides the most conservative estimate of the effect of therapy on the development of KS and reduces the bias introduced when subjects stop therapy due to adverse effects or disease progression. Because acyclovir use was often intermittent, an as-treated analysis, which incorporates the actual usage pattern of this drug, was also done. The other covariates described for the case-control analysis, including CD4 cell count before AIDS diagnosis, were also incorporated into the longitudinal analysis. Backwards stepwise regression was done using P < .05 as the criterion for remaining in the model.

Results

Case-control analysis. Cases of early KS (n = 221) and controls without early KS (n = 714) did not differ significantly with respect to age, race, or use of zidovudine, didanosine, zalcitabine, or P. carinii prophylaxis before diagnosis of AIDS (data not shown). Before diagnosis of AIDS, 35 cases (15.8%) and 131 controls (18.4%) used acyclovir for HIV infection (unadjusted odds ratio [OR] for early KS, 0.84; 95% confidence
interval [CI], 0.56–1.26; *P* = .39). Both cases and controls using acyclovir for HIV infection took the drug for a median of 2 (6-month-long) semesters (interquartile range, 1–4 for cases, 1–3 for controls; *P* = .74). Considering acyclovir use for any indication, 103 cases (46.6%) and 329 controls (46.1%) used the drug before AIDS diagnosis (unadjusted OR, 1.02; 95% CI, 0.76–1.38; *P* = .89). Cases using acyclovir for any indication took the drug during a median of 2 semesters (interquartile range, 1–4) compared with a median of 3 semesters (interquartile range, 1–5) for controls (*P* = .07). A similar proportion of cases and controls used acyclovir within 1 year of AIDS diagnosis. The median dose of acyclovir for cases and controls combined was 800 mg/day (interquartile range, 500–1200); 17 controls and 3 cases used acyclovir >3000 mg/day during at least 1 semester.

Use of acyclovir for any indication was associated with higher composite risk scores for KS (*P* < .01, Mantel-Haenszel *χ*² for trend) as was use of acyclovir for HIV infection (*P* = .055). Consequently, we adjusted for composite risk score in logistic regression models but found little impact on the lack of association between acyclovir use and early KS (OR for acyclovir use for HIV, 0.77; 95% CI, 0.51–1.17; *P* = .22; OR for acyclovir use for any indication, 0.92; 95% CI, 0.68–1.26; *P* = .62). Other logistic models incorporating CD4 cell count before AIDS, year of AIDS diagnosis, and smoking history [12] yielded similar results. Restricting the definition of acyclovir use to those using the drug within 1 year of AIDS diagnosis or to those using acyclovir for at least two study visits also yielded similar results.

**Longitudinal analysis.** We fitted intention-to-treat Cox proportional hazards models to assess the association of treatment with acyclovir and the development of late KS. Acyclovir use had no statistically significant protective association with late KS in univariate proportional hazards models (data not shown). In multivariate models (figure 2), adjustment for the composite risk score for KS (relative risk [RR], 1.24; 95% CI, 1.13–1.35; *P* < .001) and CD4 cell count before AIDS (RR, 0.72 per 100 CD4 cells/mm³; 95% CI, 0.60–0.86; *P* < .001) yielded RRs of late KS of 0.84 (95% CI, 0.54–1.30; *P* = .43) for acyclovir use for HIV and 0.94 (95% CI, 0.61–1.45; *P* = .79) for acyclovir use for any indication. Restricting the analysis to participants taking zidovudine yielded similar results.

We also conducted as-treated analyses that took into account intermittent use of acyclovir, as opposed to the intention-to-treat analyses in which acyclovir use, once initiated, was assumed to continue until death or censoring. In multivariate models adjusting for the composite risk score for KS and CD4 cell count before AIDS, neither acyclovir use for HIV (RR, 0.92; 95% CI, 0.55–1.54; *P* = .75) nor acyclovir use for any indication (RR, 1.05; 95% CI, 0.70–1.58; *P* = .81) was associated with late KS. To explore whether prolonged use of acyclovir was associated with a reduced risk of late KS, we modeled acyclovir use with time-dependent covariates denoting the cumulative number of semesters using acyclovir either for HIV or for any indication. There was no association between the number of semesters of acyclovir use and late KS.

Since ganciclovir and foscamet are used almost exclusively to treat CMV disease, we fitted a separate multivariate model for the development of late KS that included only patients with CMV disease (n = 223), 57 of whom developed late KS. In this model, which adjusted for the composite risk score for KS and use of *P. carinii* prophylaxis, neither ganciclovir use (RR, 0.56; 95% CI, 0.22–1.44; *P* = .38) nor foscamet use (RR, 0.40; 95% CI, 0.051–3.10; *P* = .38) were significantly associated with a lower risk of late KS (figure 2). However, the point estimates and lower bounds of the 95% CIs were such that a clinically important protective effect of either drug could not be ruled out.

**Discussion**

We found no association between acyclovir use and the development of KS as an early or late manifestation of AIDS in the Multicenter AIDS Cohort Study. This finding is not unexpected for several reasons. In a previous study in this cohort [8], acyclovir use was not associated with reduction in risk of AIDS-defining illnesses, including KS. Depending on the indications, acyclovir may have been used intermittently and at relatively low dosages (typically 600–800 mg/day), which may limit its effectiveness for viral prophylaxis or sup-
pression. In addition, DNA sequences from the putative herpesvirus associated with KS (KSHV) are homologous to Epstein-Barr virus (EBV) and herpesvirus saimiri [3]. Acyclovir inhibits EBV replication in vitro in productively infected cells but has no effect in latently infected cells [13]. The activity of acyclovir against herpesvirus saimiri has not been reported to our knowledge. If, as an oncogenic virus, KSHV produces a latent infection, acyclovir may have little activity against it.

We found protective associations between ganciclovir use (RR, 0.56) and foscarnet use (RR, 0.40) and the development of KS as a later manifestation of AIDS. However, neither of these associations was statistically significant, and this study did not have sufficient statistical power to give more precise estimates of the magnitudes of the potential protective associations. Only 57 men developed KS after a diagnosis of CMV disease, and ganciclovir and foscarnet were used almost exclusively in men with CMV disease. In contrast, analysis of data from the Adult/Adolescent Spectrum of Disease Study Group [14] showed a statistically significant protective association (RR, 0.3) between foscarnet use, but not ganciclovir use, and the development of KS. Furthermore, foscarnet use has been associated with a regression of KS lesions in a small case series [15]. However, foscarnet has significant toxicities and must be given intravenously, making it impractical as a prophylactic or suppressive agent for KS, even if its efficacy were proven.

Further evaluation of antiviral drugs in prophylaxis or treatment of KS would be facilitated by the propagation of KSHV in culture. Meanwhile, epidemiologic studies of patients in other observational studies and analyses from completed clinical trials of drugs with activity against herpesviruses may help direct future research in KS.

Investigators in the Multicenter AIDS Cohort Study


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References