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ADVANCES IN ANTIRETROVIRAL THERAPY:

DATA PRESENTED AT THE 16TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS

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ABSTRACT

The 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009), an annual HIV conference with the stated mission to provide a forum for basic scientists and clinicians to present, discuss and critique their investigations into the biology and epidemiology of human retroviruses and the diseases they produce, took place on February 8-11, 2009 in Montreal, Canada. This article focuses on presentations at the conference that directly deal with antiretroviral therapy (ART).

INTRODUCTION

The Conference on Retroviruses and Opportunistic Infections (CROI) is a premiere annual HIV conference with the stated mission to provide a forum for basic scientists and clinicians to present, discuss and critique their investigations into the biology and epidemiology of human retroviruses and the diseases they produce, with the ultimate goal of translating laboratory and clinical research into progress against the AIDS epidemic. The 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009) took place on February 8-11, 2009 in Montreal, Canada. This article focuses on presentations at the conference that directly deal with antiretroviral therapy (ART). The author is solely responsible for the selection of topics and presentations to be included in this report. This report is not an endorsed activity of CROI itself.

WHEN TO START ANTIRETROVIRAL THERAPY?

The optimal time for initiating ART in asymptomatic HIV-infected individuals remains undefined. The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents currently recommends initiation of ART in patients with a history of AIDS-defining illness or with a CD4 T-cell count of < 350 cells/mm^3. However, there is a growing interest in exploring the benefits of earlier initiation of ART. Two studies addressing this issue were presented at CROI 2009.

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a collaboration of cohorts that includes over 90,000 patients from the U.S. and Canada. Kitahata and colleagues presented results of their comparison of survival between patients who initiate combination ART and those who defer treatment (1). Included in the analyses were 9,155 patients with a CD4 count > 500 cells/mm^3 between 1996 and 2006, who did not have a diagnosis of AIDS and had never received ART. These patients contributed 28,032 person-years of follow-up. A total of 2,616 patients (29%) initiated ART at a CD4 count > 500 cells/mm^3 (median 674 cells/mm^3), while the remaining 6,539 (71%) deferred treatment until the CD4 cell count fell below 500 cells/mm^3 (median 390 cells/mm^3). Among those who deferred ART, 410 died, compared to 196 deaths among those who initiated therapy at a CD4 count > 500 cells/mm^3 (hazard ratio [HR]: 1.4; 95% confidence interval [CI]: 1.1-1.7; P = 0.008). Thus, patients who deferred ART at a CD4 count > 500 cells/mm^3 had a 60% higher risk of mortality.

Sterne and colleagues from the "When to start consortium" presented results from their analysis of data from 15 prospective observational cohorts participating in the Antiretroviral Therapy (ART) Cohort Collaboration, a collaboration of cohort studies from Europe and North America established with the aim of describing the prognosis of antiretroviral-naïve patients starting combination therapy (2). Estimates of distributions of lead times from the first CD4 cell

count measurement in an upper range to the upper threshold of a lower range, as well as unseen AIDS and death events in the absence of treatment, were made using data from seven cohort studies that followed patients during the era before the introduction of combination ART. The rates of AIDS and death, and death, were compared between deferral and immediate initiation of antiretroviral therapy in adjacent CD4 cell count ranges. A total of 24,444 patients from the ART Cohort Collaboration with 81,071 person-years of follow-up were included in the analysis, and 21,247 patients from the pre-combination ART therapy era with 68,253 person-years of follow-up contributed data for the lead time and event estimates in the absence of treatment. In this analysis, deferring antiretroviral therapy until a CD4 cell count of 251-350 cells/mm^3 was associated with higher rates of the combined endpoint of AIDS and death compared to starting therapy in the range of 351-450 cells/mm^3 (HR: 1.28; 95% CI: 1.04–1.57). The impact on mortality alone was less marked (HR: 1.13; 95% CI: 0.80-1.60).

ABACAVIR AND CARDIOVASCULAR COMPLICATIONS

The dramatic decline in HIV-associated morbidity and mortality due to combination antiretroviral therapy has changed HIV into a chronic lifelong disease. As HIV-infected individuals live longer, the so-called diseases of aging, such as cardiovascular disease, have now become a focus of great attention in the management of HIV-infected patients. The preponderance of current evidence suggests that HIV-infected individuals are at increased risk of cardiovascular disease compared with non-HIV-infected individuals. The potential contribution of individual antiretroviral drugs and classes of antiretroviral drugs has become a subject of intense debate. The first report that implicated the nucleoside reverse transcriptase inhibitor abacavir as a cause of an increased risk of cardiovascular disease emerged from the D:A:D study (Data Collection on Adverse Events on Anti-HIV Drugs) (3). This report suggested that current or recent (within the last 6 months) use of abacavir was associated with an excess risk of myocardial infarction.

The D:A:D study group presented an update on their investigations exploring associations between specific antiretroviral drugs and the risk of myocardial infarction (4). In their analysis of data on 33,308 patients from 11 prospectively followed cohorts, recent exposure to abacavir (relative rate [RR]: 1.68; 95% CI: 1.33-2.13) or didanosine (RR: 1.41; 95% CI: 1.09-1.82) continued to be associated with an increased risk of myocardial infarction. Additionally, cumulative exposure to the protease inhibitors lopinavir/ritonavir (RR: 1.13; 95% CI: 1.05-1.21) or indinavir (RR: 1.12; 95% CI: 1.07-1.18) was associated with an increased risk of myocardial infarction. However, there were no statistically significant associations between recent or cumulative use of tenofovir, dideoxycytidine, zidovudine, stavudine, lamivudine, nevirapine, efavirenz, nelfinavir or saquinavir and myocardial infarction risk.

Two additional studies evaluated the association between abacavir and the risk of myocardial infarction. ACTG A5001 analyzed data from 3,205 patients randomized to their first ART regimen in one of five ACTG studies (5). Extended follow-up data were available for a subset of 2,164 patients through the ACTG Longitudinal Linked Randomized Trials (ALLRT) protocol; 781 patients were randomized to ABC. Sixty-three severe cardiovascular disease events, including 27 myocardial infarctions, were identified. However, there was no significant association between recent use of abacavir and either myocardial infarction or severe cardiovascular disease.

The clinical EPI group of the French Hospital Database on HIV presented their analysis of the effect of exposure to specific nucleoside reverse transcriptase inhibitors and protease inhibitors on the risk of myocardial infarction in the French Hospital Database on HIV using a nested case-control study (6). Included in the analysis were patients enrolled in the database who had a first myocardial infarction prospectively reported between January 2000 and December 2006 (n = 286). As many as five age-, sex- and clinical center-matched controls with no history of myocardial infarction were selected for each case (n = 865). Recent exposure to abacavir was significantly associated with an increased risk of myocardial infarction (odds ratio [OR]: 2.19; 95% CI: 1.19-4.02). No other nucleoside reverse transcriptase inhibitor was associated with an increased risk of myocardial infarction. Cumulative exposure to the protease inhibitors lopinavir (OR: 1.38/year; 95% CI: 1.10-1.74) and amprenavir/fosamprenavir (OR: 1.55/year; 95% CI: 1.20-1.99) was also significantly associated with an increased risk of myocardial infarction.

A number of other studies investigated the possible association of abacavir with increased levels of inflammatory and other markers in an attempt to establish a mechanism for the increased risk of myocardial infarction that has been reported with the use of abacavir (7-11). These studies are summarized in Table I.

THE DEMISE OF INTERLEUKIN-2

The potential utility of interleukin-2 (IL-2) to augment immune function has been extensively evaluated for a number of years. While most studies of IL-2 have shown that it induces significant increases in CD4 cell counts in HIV-infected patients, definitive results from the two large randomized clinical trials that investigated whether these CD4 cell increments will result in tangible clinical benefits were eagerly anticipated. The final results of these studies were presented at CROI 2009.

ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) compared the efficacy of subcutaneous recombinant IL-2 plus combination ART versus combination ART alone on the rates of HIV disease progression, including death (12). ESPRIT enrolled 4,111 patients (2,071 receiving IL-2 plus ART and 2,040 receiving ART alone) who were followed up for a median of 7 years. The IL-2 regimen consisted of three 5-day cycles at 8-week intervals, with additional cycles recommended to maintain the CD4 cell count > twice baseline or ≥ 1000 cells/mm^3. At study entry, median CD4 count was 457 cells/mm^3. The IL-2 group had significantly greater CD4 cell count increases than the ART alone group, the difference in CD4 cell count at 6 years being 128 cells/mm^3 ($P < 0.001$). However, these CD4 count increases did not result in any clinical benefit and IL-2 was associated with more grade 4 clinical events.

SILCAAT (Subcutaneous IL-2 in HIV infected patients with Low CD4$^+$ counts receiving Active Antiretroviral Therapy) compared the effects of subcutaneous recombinant IL-2 plus combination ART versus combination ART alone on disease progression and death in HIV-infected patients on stable highly active antiretroviral therapy (HAART) who had a CD4$^+$ cell count between 50 and 299 cells/mm^3

Table I. *Studies on the association of abacavir with inflammatory and other markers.*

Study or author	Primary aim of study	Design	Result
ACTG 5095 (7)	Evaluation of 96-week effects of efavirenz-based antiretroviral therapy with or without abacavir on levels of high-sensitivity C-reactive protein (hs-CRP)	Assay of hs-CRP in banked baseline and 96-week serum; N = 100	Efavirenz-based suppressive therapy did not improve hs-CRP levels; the inclusion of hs-CRP did not have a significant effect on hs-CRP.
WIHS/MACS (8)	Assessment of hs-CRP, D-dimer and IL-6 at baseline and at the first visit at which abacavir use was reported	Case-control study, MACS and WIHS participants who initiated abacavir either at or after first HAART initiation vs. matched abacavir-unexposed persons; N = 1,016	The use of abacavir was not independently associated with elevated plasma levels of hs-CRP, IL-6 or D-dimer
Hsue et al. (9)	Comparison of endothelial function in patients on suppressive antiretroviral therapy with or without abacavir	Measurement of flow-mediated vasodilatation of the brachial artery; N = 61, 30 of whom were on abacavir-containing therapy	Current use of abacavir was independently associated with impaired endothelial function
Satchell et al. (10)	To compare platelet function in HIV-1-infected individuals on abacavir-containing regimens vs. those on regimens without abacavir	Time-dependent platelet aggregation was measured upon exposure to increasing concentrations of several platelet agonists; n = 38 abacavir group, n = 20 nonabacavir group	Platelet reactivity was consistently increased in the abacavir group
HEAT study (11)	To compare the effects of initiating abacavir/lamivudine and tenofovir/emtricitabine on three inflammatory biomarkers – hs-CRP, IL-6 and soluble vascular cell adhesion molecule 1 (sV-CAM 1)	Retrospective analysis of paired plasma samples from HEAT study subjects for hs-CRP, IL-6 and sV-CAM 1 at baseline, weeks 48 and 96; n = 243 for the abacavir group, n = 233 for the tenofovir group	Declines from baseline in sV-CAM 1, IL-6 and hs-CRP concentrations were observed at weeks 48 and 96 in both groups; there was no difference in the degree of reduction between arms for any of the biomarkers

and a viral load < 10,000 copies/mL (13). The IL-2 regimen consisted of six 5-day cycles at 8-week intervals, with additional cycles recommended to maintain the CD4 cell count an average of 150 cells above baseline. SILCAAT enrolled 1,695 patients (849 IL-2, 846 control) with a median CD4 cell count of 202 cells/mm^3, who were followed for a median of 7.6 years. Similar to what was observed in ESPRIT, IL-2 resulted in a significantly greater CD4 cell increase, with a difference in CD4 cell count at 6 years of 37 cells/mm^3 ($P < 0.001$). However, this CD4 cell count increase was not associated with a decline in opportunistic diseases or death. Unlike ESPRIT, IL-2 was not associated with more grade 4 clinical events in SILCAAT.

MICROBICIDES

Prior to CROI 2009, clinical trials of microbicides had been uniformly unsuccessful. Results of HPTN 035 offered the first successful outcome from a microbicide clinical trial. HPTN 035 was a phase II/IIB randomized, placebo-controlled trial that assessed the safety and efficacy of two microbicides, BufferGel and 0.5% PRO-2000/5 gel, for the prevention of male-to-female HIV transmission (14). The study was conducted in several African countries, as well as the U.S. A total of 3,099 women were randomized to four groups: no gel, placebo gel, BufferGel or 0.5% PRO-2000/5 gel. Participants were followed for an average of 20.4 months. Gel use, condom use and HIV infection were assessed quarterly. Adverse events, adherence to gel use and participant retention rates were similar across the relevant groups. HIV incidence in each active gel arm was compared to each control arm. However, condom use was higher in the no-gel arm: 81% vs. 72% ($P < 0.05$). In an intent-to-treat analysis, HPTN 035 found a 30% protective effect from HIV acquisition for 0.5% PRO-2000/5 gel compared to no gel (HR: 0.7; 95% CI: 0.5-1.1; $P = 0.10$). No protective effect was observed for either BufferGel or placebo gel.

NEW PHARMACOKINETIC ENHANCERS

The use of low-dose ritonavir to enhance the pharmacokinetics of protease inhibitors, i.e., boosting, so that they become more effective and more convenient to take (fewer pills, longer dosing intervals) has become standard clinical practice. All currently licensed protease inhibitors, with the exception of nelfinavir, are commonly prescribed as booster agents. Such use of ritonavir is not without its controversies, both from a price and an incremental toxicity standpoint. Preliminary data for two new products with pharmacokinetic-enhancing properties but without antiviral activity were reported at CROI 2009.

GS-9350

Data from a phase I study of the new cytochrome P450 3A inhibitor GS-9350 were presented (15). Study GS-216-0101 compared the safety, tolerability, pharmacokinetics and boosting capacity of three doses of GS-9350 (50, 100 and 200 mg) to 100 mg ritonavir, all given once daily, in HIV-negative volunteers (n = 18 per cohort) over a 14-day period. GS-9350 showed no antiviral activity at concentrations up to 90 µM. Its in vitro effects on adipocytes and proteasome activity were lower than for ritonavir 100 mg. GS-9350 doses of 100 and 200 mg demonstrated inhibition of midazolam clearance (a marker for CYP3A inhibition) similar to ritonavir 100 mg.

SPI-452

Results of preclinical and early clinical evaluation of SPI-452, another new pharmacokinetic-enhancing agent, were also presented (16). Similar to GS-9350, SPI-452 does not appear to have inherent antiviral activity. In the preclinical in vitro studies, SPI-452 exhibited CYP3A-inhibitory activity similar to ritonavir. This CYP3A-inhibitory effect of SPI-452 was also confirmed in a series of single-dose in vivo animal studies, in which SPI-452 enhanced the systemic exposure of coadministered saquinavir, lopinavir and atazanavir.

Two clinical studies of SPI-452 were also presented. Study 0452-001, the first-in-human clinical study of SPI-452, evaluated the safety, tolerability and pharmacokinetics of single ascending doses of SPI-452 administered alone and in combination with 1000 mg saquinavir in 58 healthy volunteers. The study had two phases. Phase I used escalating doses of SPI-452 in six cohorts (25, 50, 100, 200, 400 and 600 mg). In phase II, participants were randomized to SPI-452 (50 or 200 mg) plus saquinavir (1000 mg), saquinavir (1000 mg) alone or placebo. SPI-452 substantially increased the mean exposure levels of saquinavir. Headache was the most common adverse event.

The pharmacokinetic profile of multiple doses of SPI-452 in combination with darunavir or atazanavir was evaluated in 67 healthy volunteers in a proof-of-concept study. SPI-452 achieved steady state by day 14. Plasma concentrations of darunavir at 24 h were enhanced as much as 29-fold and those of atazanavir as much as 13-fold when coadministered with SPI-452. The most frequent adverse events reported were headache, nausea/emesis and diarrhea.

SUMMARY

HIV medicine continues to be a rapidly and ever-evolving discipline. Thirteen years after the advent of HAART, the optimal time to initiate ART in asymptomatic patients and what drugs to start with remain not fully defined. While the antiretroviral drug development pipeline has been relatively robust to date, CROI 2009 hosted the introduction of two products without inherent antiviral activity but with promising potential for the development of new coformulated antiretroviral products. Finally, debate continues regarding the relative contribution of individual antiretroviral drugs and drug classes to long-term complications of HIV, such as cardiovascular disease, and its treatment.

DISCLOSURE

The author states no conflicts of interest.

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