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Three-Year Safety and Efficacy of Vicriviroc, a CCR5 Antagonist, in HIV-1-Infected, Treatment-Experienced Patients

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Abstract

Background—Vicriviroc, an investigational CCR5 antagonist, demonstrated short-term safety and antiretroviral activity.

Methods—Phase 2, double-blind, randomized study of vicriviroc in treatment-experienced subjects with CCR5-using HIV-1. Vicriviroc (5, 10 or 15 mg) or placebo was added to a failing regimen with optimization of background antiretroviral medications at day 14. Subjects experiencing virologic failure and subjects completing 48 weeks were offered open-label vicriviroc.

Results—118 subjects were randomized. Virologic failure ($<1 \log_{10}$ decline in HIV-1 RNA ≥ 16 weeks post-randomization) occurred by week 48 in 24/28 (86%), 12/30 (40%), 8/30 (27%), 10/30 (33%) of subjects randomized to placebo, 5, 10 and 15 mg respectively. Overall, 113 subjects received vicriviroc at randomization or after virologic failure, and 52 (46%) achieved HIV-1 RNA <50 copies/mL within 24 weeks. Through 3 years, 49% of those achieving suppression did not experience confirmed viral rebound. Dual or mixed-tropic HIV-1 was detected in 33 (29%). Vicriviroc resistance (progressive decrease in maximal percentage inhibition on phenotypic testing) was detected in 6 subjects. Nine subjects discontinued vicriviroc due to adverse events.

Conclusions—Vicriviroc appears safe and demonstrates sustained virologic suppression through 3 years of follow-up. Further trials of vicriviroc will establish its clinical utility for the treatment of HIV-1 infection.

Keywords

HIV-1; CCR5 antagonist; vicriviroc; antiretroviral therapy

INTRODUCTION

Current treatment guidelines suggest that HIV-1-infected patients should receive at least two (and preferably 3) fully active agents when constructing a new antiretroviral regimen following treatment failure to achieve maximal virologic suppression [1]. Antiretroviral agents in new drug classes are especially useful because there is no concern about cross-resistance resulting from virologic failure to prior regimens, as substantiated by clinical trial results for recently approved agents in new drug classes [2–5].

CCR5 antagonists have established virologic activity in patients with HIV-1 strains using CCR5 as the exclusive coreceptor for entry into CD4+ T-cells (R5 virus) [4,6]. There is little to no activity in subjects harboring dual-tropic or mixed populations of HIV-1 using both CCR5 and CXCR4 (DM virus) or HIV-1 populations using CXCR4 alone (X4 virus) [7]. Vicriviroc is an investigational CCR5 antagonist with demonstrated antiretroviral activity [6,8,9]. Vicriviroc is a substrate for the 3A4 isozyme of the hepatic cytochrome P450 enzyme system; therefore, the plasma concentrations of vicriviroc are increased 2–6 fold in the presence of ritonavir [10]. ACTG A5211 is a phase 2 trial of vicriviroc in HIV-1-infected patients who experienced failure of prior antiretroviral regimens and were experiencing failure of a ritonavir-containing regimen. The primary outcome, change in plasma HIV-1 RNA level 14 days after randomization, and the week 24 results were reported previously [6]. This manuscript reports the 3-year follow-up of participants to

evaluate the long-term safety and efficacy of vicriviroc, an investigational agent in a new drug class.

METHODS

Study subjects

Eligible subjects were HIV-1-infected adults with R5 HIV-1 by the original Trofile Assay (Monogram Biosciences, South San Francisco, CA), plasma HIV-1 RNA $\geq 5,000$ copies/mL, and prior virologic failure to an antiretroviral regimen including at least 3 drugs and currently receiving a ritonavir-containing antiretroviral regimen. The study was approved by the institutional review boards at each of the participating institutions. Written, informed consent was obtained from study participants. Human experimentation guidelines of the US Department of the Health and Human Services were followed in the conduct of this research.

Study design

Details of the design of A5211 are available elsewhere [6]. A5211 was a double-blind placebo-controlled, 48-week study with extended follow-up for safety in treatment-experienced patients conducted by 33 sites of the AIDS Clinical Trials Group (ACTG). At entry, subjects were randomized to vicriviroc (5 mg, 10 mg, 15mg, Schering-Plough, Kenilworth, NJ) or placebo added to their currently failing antiretroviral regimen. The primary endpoint of this study was the change in plasma HIV-1 RNA after 2 weeks of vicriviroc use. After 2 weeks, subjects optimized their background ART regimen based on history, genotypic (TRUGENE; Bayer Healthcare, Tarrytown, NY) and phenotypic (PhenoSense; Monogram Biosciences) drug resistance testing. Genotypic Sensitivity Score (GSS) [11] and Phenotypic Sensitivity Score (PSS) [12,13] for all drugs in the subject's background regimen initiated at day 14 were calculated. Study visits occurred at entry, days 3, 7, 14, week 3, week 4, every 4 weeks through week 24, every 8 weeks through week 48. Coreceptor tropism assays (Trofile, Monogram Biosciences) were performed on subjects with plasma HIV-1 RNA levels >1000 copies/mL at entry, day 14, week 24, week 48, and confirmation of virologic failure, if applicable. Adverse events were assessed by the site investigators and graded according to the toxicity scale of the Division of AIDS, National Institutes of Health [14].

The baseline HIV-1 RNA level was determined as the geometric mean of the pre-entry and entry levels. The date of virologic failure was defined as the first of two consecutive plasma HIV-1 RNA levels $<1 \log_{10}$ copies/mL below baseline occurring at week 16 or later. If virologic failure occurred, the subject could request unblinding and re-optimize the antiretroviral regimen based on treatment history and repeat drug resistance testing. In addition, under earlier versions of the protocol, subjects in the placebo group or 5 mg group could receive vicriviroc 10 mg daily; subjects in the 10 mg or 15 mg group continued vicriviroc at the same dose. Following the discontinuation of the 5 mg dose, the protocol was modified to allow all subjects to receive 15 mg of vicriviroc after virologic failure.

Subjects with a confirmed change in coreceptor use from R5 to DM or X4-using virus were initially required to discontinue vicriviroc, but a protocol amendment allowed such subjects to continue vicriviroc use if they had not experienced virologic failure or a decrease in CD4 count below baseline

At week 48, all subjects were offered open-label vicriviroc 15 mg daily through a companion protocol to provide long-term access to vicriviroc and long-term follow-up of vicriviroc use. The study, P04100, was sponsored by Schering-Plough and conducted at the same clinical trials sites as A5211. Subjects were allowed to modify their background ART

regimen at any point during that trial. Coreceptor tropism was determined 8 weeks after entry to P04100 and at confirmation of virologic failure if the plasma HIV-1 RNA was ≥ 500 copies/mL. P04100 was modified on 30 November 2007 to increase the vicriviroc dose to 30 mg daily based on results from another clinical trial [8].

Study Monitoring

As previously reported [6], the Study Monitoring Committee (SMC) modified A5211 on 6 October 2005 to discontinue the 5 mg dose of vicriviroc based on trends towards suboptimal virologic responses and more emergence of DM/X4 virus. These subjects were unblinded and offered open-label vicriviroc at 15 mg daily. All study subjects were unblinded on 6 March 2006 after the SMC raised concerns about the occurrence of malignancies including 4 lymphomas and 1 gastrointestinal cancer in subjects receiving vicriviroc. All subjects who received vicriviroc were asked to remain in study follow-up for ascertainment of malignancy or death for a total of 5 years regardless of whether they remained on vicriviroc.

Statistics

The analyses of HIV-1 RNA, CD4 count, and co-receptor usage are based on data obtained during the 48 weeks of follow-up in A5211, plus the period of follow-up in P04100 during which subjects were receiving the 15mg dose of vicriviroc. The analyses of malignancies and deaths are based on all available follow-up in A5211 and P04100 through February 22, 2009. Time to virologic failure analysis used an intention-to-treat approach and the log-rank test. For all analyses, p -values < 0.05 were considered significant.

RESULTS

Baseline subject characteristics and disposition

A total of 118 subjects were enrolled in ACTG 5211. Baseline characteristics are summarized in Table 1. Study subjects were highly antiretroviral treatment-experienced: 33% had prior use of enfuvirtide, and the median [inter-quartile range (IQR)] GSS and PSS to the optimized background regimen taken from day 14 were 0.78 [0.33, 1.53] and 1.88 [1.00, 2.73]. At week 48, a non-random subset of subjects, 79 of 118 (67%), were enrolled in the long-term follow-up study (P04100). 79 received open-label vicriviroc 15 mg daily (Table 1). Thirty (38%) experienced prior virologic failure on A5211 (compared to 46% of the 118 subjects randomized in A5211). The disposition of study subjects through 3 years of follow-up is shown in Table 2.

Virologic and Immunologic results

During the first 48 weeks of study follow-up, virologic failure occurred in 24 of 28 (86%) subjects randomized to placebo, 12 of 30 (40%) in the 5 mg vicriviroc group, 8 of 30 (27%) in the 10 mg group and 10 of 30 (33%) in the 15 mg group. The time to virologic failure was significantly longer for each of the three vicriviroc groups compared to placebo ($P = .01$ for 5 mg vs. placebo, $P < .001$ for 10 mg vs. placebo and 15 mg vs. placebo; Figure 1). Using the last-observation-carried-forward approach, the mean reduction in $\log_{10}$ HIV-1 RNA level from baseline to week 48 was -1.89 and -1.47 $\log_{10}$ copies/mL for the 10 mg and 15 mg group, respectively ($P = 0.18$ comparing 10 mg vs. 15 mg), and the mean change in CD4 count from baseline to Week 48 was 126 and 134 cells/mm³ for the 10 mg and the 15 mg group, respectively ($P > 0.5$ comparing 10 mg vs. 15 mg). The change in HIV-1 RNA and CD4 count were not calculated for the placebo and 5 mg groups due to the high discontinuation rate of randomized treatment prior to week 48.

At entry into the long-term follow-up study (48 weeks after randomization to A5211), 35 (44%) of the 79 subjects who received vicriviroc in P04100 had plasma HIV-1 RNA < 50

copies/mL, 19 (24%) had 50 to 399 copies/mL and 25 (32%) were ≥ 400 copies/mL; at week 96 and 144, 37 (47%) and 44 (56%) were < 50 copies/mL. Of note, 12 subjects had a protocol-mandated increase of vicriviroc from 15 mg to 30 mg prior to week 144. For this analysis, the last observed plasma HIV-1 RNA measurement while receiving 15 mg was carried forward. The increases in mean CD4 counts from entry to week 48 were sustained through 3 years post-randomization and did not change appreciably during the long-term follow-up study.

We conducted a post-hoc analysis of the time to viral rebound (confirmed plasma HIV-1 RNA > 50 copies/mL) after achieving an HIV-1 RNA level < 50 copies/mL within 24 weeks of initiating a first vicriviroc-containing regimen (including subjects originally randomized to placebo who later initiated a vicriviroc-containing regimen). Overall, 113 of 118 subjects (96%) initiated vicriviroc at some point during the study. 52 (46%) achieved a plasma HIV-1 RNA < 50 copies/mL within 24 weeks of initiating vicriviroc. One subject who achieved virologic suppression had DM virus at entry to A5211 and was excluded from the analysis of time to viral rebound. The time to viral rebound for the remaining 51 subjects is shown in Figure 2. The Kaplan-Meier estimate of no viral rebound at week 144 was 49% for those achieving virologic suppression on a vicriviroc-containing regimen. The risk of viral rebound was highest in the first 48 weeks after virologic suppression; there was a lower risk of virologic rebound subsequently.

Detection of X4 virus during vicriviroc use and reduced susceptibility to vicriviroc

Of the 90 subjects randomized to vicriviroc, 10 (11%) had DM virus on repeat coreceptor tropism at the time of initiating vicriviroc and 18 (20%) had emergence of DM virus after vicriviroc initiation: 8 at day 14, 2 at week 8, 3 at week 24, 2 at week 48, and 3 between weeks 48 week 72. Among 23 subjects randomized to placebo who later initiated vicriviroc, 5 (22%) had emergence of DM virus with vicriviroc use. One of eight subjects with emergence of DM virus after 14 days of vicriviroc use achieved subsequent plasma HIV-1 RNA < 50 copies/mL with the change in background ART at day 14. Three subjects had achieved a plasma HIV-1 RNA < 50 copies/mL prior to detection of DM virus.

Among subjects who experienced virologic failure, no significant decrease in the PSS and GSS for the background regimen was found, and no significant increase in IC₅₀ (half maximal inhibitory concentration) fold change for vicriviroc was detected on repeat testing at the time of virologic failure. With ongoing HIV-1 viremia and continued vicriviroc use, four subjects out of 113 (4%) who ever received vicriviroc had clear emergence of reduced susceptibility to vicriviroc manifested by a progressive decrease in the maximal percent inhibition (MPI) to $< 50\%$ on phenotypic drug susceptibility assay. This occurred after 24 weeks (previously reported [15]), 2 years, 3 years, and 3 years of vicriviroc use respectively (see Figure 3). Of note, the GSS score for the background ART regimen initiated at day 14 was < 1 for all 4 subjects. Two other subjects of the 113 ever receiving vicriviroc (2%) had smaller reductions in MPI (73% and 77%) that did not progress over time.

Adverse events

Sixty-one of 118 subjects (52%) experienced a grade 3 or 4 clinical or laboratory event prior to week 48. This was not significantly different between the vicriviroc arms and placebo, or among the vicriviroc arms. Through 3 years of follow-up, 9 of 113 subjects ever initiating vicriviroc (8%) experienced adverse events that led to premature discontinuation of vicriviroc (allergic reaction, cardiopulmonary arrest resulting in death, lipase elevation, Hodgkin's Disease (n=2), mucormycosis, nausea/emesis (n=2), and neuropathy) and one subject experienced lipase elevations that led to discontinuation of placebo. The allergic

reaction was characterized by rash and occurred in a subject who initiated vicriviroc less than 14 days earlier prior to changing the background ART.

During the 486 patient-years of follow-up for the 113 subjects who ever received vicriviroc, 12 (11%) were diagnosed with 13 malignancies (2.67 per 100 patient-years) after receiving vicriviroc, and one malignancy was diagnosed in a subject receiving placebo. These case descriptions are listed in Table 3. Five of these subjects died as a result of these malignancies. Nine of 13 malignancies occurred while subjects were receiving vicriviroc, and four were diagnosed after subjects discontinued vicriviroc. The case descriptions of 4 subjects with lymphomas, 2 of whom had a prior history of lymphoma, are discussed in detail elsewhere [16]

Thirteen (11%) of the subjects are known to have died. The causes of death in addition to the 5 subjects who died of malignancy were cardiopulmonary arrest (n=2), chronic obstructive pulmonary disease, cytomegalovirus encephalitis, end-stage HIV, gastrointestinal hemorrhage, mucormycosis, and progressive multifocal leukoencephalopathy.

DISCUSSION

This clinical trial establishes the sustained safety, tolerability, and virologic activity of vicriviroc, an investigational oral CCR5 antagonist, through 3 years of follow-up. This study represents the longest available follow-up for patients taking a CCR5 antagonist. In total, 46% of subjects initiating a vicriviroc regimen achieved virologic suppression <50 copies/mL, and this suppression was durable in half of them through a total of 3 years of follow-up. This was a highly treatment-experienced population; the background ART regimens for study subjects were of limited predicted effectiveness-56% had a genotypic sensitivity score of ≤ 1 . Of note, newer antiretroviral drugs (e.g. darunavir, etravirine, raltegravir) were not used in this study. Vicriviroc appeared well-tolerated during 3 years of follow-up with low rates of discontinuation due to adverse events.

The major limitation to the clinical use of CCR5 antagonists is the frequency of subjects with viral populations using both CCR5 and CXCR4 as the coreceptor for viral entry into CD4⁺ T-cells [17]. Previous reports from A5211 found that 50% of the treatment-experienced subjects screened for eligibility in this trial had DM or X4 virus [18]. Approximately 30% of subjects receiving vicriviroc had emergence of DM virus. The emergence of DM virus occurred mostly during the first 24 weeks after initiating vicriviroc, and was uncommon in those who had virologic rebound after achieving virologic suppression of <50 copies/mL. This finding is consistent with the emergence of DM virus from pre-existing low-abundance DM variants rather than through mutational evolution of viral species under pressure from CCR5 antagonists [19,20]. Resistance to vicriviroc developed uncommonly in this study, and was documented in 6 subjects out of 113 ever initiating vicriviroc (5%). These subjects experienced prolonged HIV-1 viremia while receiving vicriviroc. Resistance was characterized by a decrease in MPI rather than a change in IC₅₀ (see Figure 3). The likely reason for virologic failure in subjects without emergence of DM virus or phenotypic resistance was lack of an effective optimized background regimen.

CCR5 antagonists do not appear to have robust virologic activity in patients harboring DM or X4 virus [7,8]. DM and X4 viruses are found more commonly among patients with more advanced HIV disease (e.g., lower CD4 counts and prior virologic failure) [17,18,21]. The biology of tropism evolution over time suggests that CCR5 antagonists may have greater clinical utility for patients earlier in the course of their HIV infection than for those who

were studied in this protocol; however, clinical trials data to support this assertion are limited [9,22]. Other studies of treatment-experienced patients have found the optimal dose of vicriviroc to be 30 mg once daily given with a ritonavir-containing regimen [8]. The rates of virologic suppression are likely to be higher with the optimal dose of vicriviroc and in combination with newer antiretroviral agents.

Thirteen malignancies developed among 113 subjects who had initiated vicriviroc at some point previously. We saw a decreasing trend in the rate of malignancies since the SMC raised concerns on possible relationship between vicriviroc exposure and malignancies in March 2006. The SMC noted that the study patients in general had advanced HIV disease and that the malignancies were of diverse types. They determined that a causal link to vicriviroc could not be established. We also evaluated subjects with malignancies that were potentially Epstein-Barr Virus related (Non-Hodgkin's Lymphoma and Hodgkin's Disease) and found that EBV replication was not enhanced by vicriviroc in this subset or among ACTG 5211 subjects in general [16]. An increased number of malignancies were not found in a subsequent study of vicriviroc [9] or in much larger clinical studies of maraviroc, an FDA approved CCR5 antagonist [4].

This study has several limitations. It was conducted prior to the availability of newer antiretroviral agents such as darunavir, raltegravir and etravirine that would be expected to provide significant virologic activity in subjects such as those enrolled in A5211 [4,5,23,24]. The assay used to determine eligibility, the original Trofile, has now been replaced in clinical practice by a modified assay with enhanced sensitivity for X4 or DM viruses [25]. An accurate determination of coreceptor tropism is critical before initiating CCR5 antagonists. This protocol had several vicriviroc dose changes during its conduct – the 5 mg dose was discontinued early due to suboptimal virologic activity and all patients later had their doses increased to 15 mg. In addition, for many subjects vicriviroc was administered as the sole change in ART for 14 days. The subjects entering the long-term follow-up study were a non-random subset of A5211 subjects and were enriched for those subjects who had received virologic benefit from vicriviroc; moreover, the subjects in the long-term follow-up study were allowed to change their background ART regimen and the sustained virologic suppression cannot be attributed solely to vicriviroc.

In summary, in HIV-1-infected, treatment-experienced subjects, the CCR5 inhibitor vicriviroc together with a ritonavir-containing background antiretroviral regimen provided virologic and immunologic benefit through 3 years of follow-up. This represents the longest prospective follow-up data available for a CCR5 antagonist. Vicriviroc appeared safe and well-tolerated with low rates of discontinuation due to adverse events. Further trials of vicriviroc in combination with newer antiretroviral agents will establish the clinical utility of this drug for the treatment of HIV-1 infection.

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Figure 1.

Time to virologic failure (Intention-to-treat approach: follow-up censored at date of last available HIV-1 RNA measurement or at the date of dose increase to 15mg for subjects randomized to 5 mg)

Note: Virologic failure is defined as $<1 \log_{10}$ decline from baseline at or after 16 weeks after randomization.

Figure 2. Time to viral rebound (confirmed HIV-1 RNA >50 copies/mL) among subjects HIV-1 RNA suppressing to <50 copies/ml within 24 weeks of zidovudine initiation

Figure 3a and 3b.

Vicriviroc susceptibility of HIV-1 from a subject for whom vicriviroc-containing antiretroviral therapy failed. Vicriviroc susceptibility was examined at week 0 (study entry) (a), and after 2 years of vicriviroc use by the PhenoSense entry assay (Monogram Biosciences, South San Francisco, CA) (21).

Table 1

Baseline characteristics of the study subjects

Characteristic	Total participants in A5211 (n=118)	Participants entering P04100 (n=79)
Sex		
Men	108 (92)	74 (94)
Women	10 (8)	5 (6)
Age, median [IQR] years	46 [41, 53]	47 [42, 54]
Race, ethnicity		
White, non-Hispanic	78 (66)	52 (66)
Black, non-Hispanic	24 (20)	15 (19)
Hispanic, regardless of race	14 (12)	10 (13)
Asian/Pacific Islander	1 (1)	1 (1)
Other/unknown	1 (1)	1 (1)
IV drug use		
Never	113 (96)	74 (94)
Previously	5 (4)	5 (6)
Prior enfuvirtide use	39 (33)	23 (29)
HIV-1 RNA, median [IQR] log10 copies/mL	4.56 [4.16, 5.15]	4.5 [4.0, 5.0]
CD4 cell count, median [IQR] cells/mm ³	146 [63, 254]	159 [90, 282]
Genotypic sensitivity score of background ART planned for day 14, median [IQR]	0.78 [0.33, 1.53]	0.78 [0.33, 1.73]
Phenotypic sensitivity score of background ART planned for day 14, median [IQR]	1.88 [1.00, 2.73]	1.89 [1.00, 2.75]

Note: Values are No. (%) unless otherwise noted. IQR=inter-quartile range.

Table 2

Subject disposition through 144 weeks

	Placebo (n=28)	VCV 5 mg (n=30)	VCV 10 mg (n=30)	VCV 15 mg (=30)
Completed 48 weeks on randomized VCV dose or placebo	5	5	19	23
Dose increase or initiation of VCV due to virologic failure or protocol change prior to week 48	21	18	3	0
Premature discontinuation of randomized treatment prior to week 48	2	7	8	7
Adverse event	1	1	3	1
Detection of X4 virus	0	5	2	3
Physician or participant decision	1	1	3	3
Enrolled in long-term follow-up study at week 48	18 (64%)	18 (60%)	21 (70%)	22 (73%)
Completed 144 weeks on VCV 30 mg	8	9	18	14
Protocol-mandated increase from 15 mg to 30 mg prior to week 144	3	5	2	2
Discontinuation after week 48 and prior to week 144	7	4	1	6
Adverse event	1	2	0	0
Lost-to-follow-up	1	0	0	2
Physician or participant decision	2	2	1	2
Treatment failure	3	0	0	2

VCV=vicriviroc

Table 3

Malignancies occurring in study subjects

Subject	Malignancy	Prior VCV exposure in weeks	Receipt of VCV at malignancy diagnosis	CD4 prior to malignancy diagnosis (cells/mm ³)	Plasma HIV-1 RNA level prior to malignancy diagnosis (copies/mL)	Malignancy resulted in death
1	Basal cell carcinoma of the nose	102 weeks	Yes	78	822	No
2	Diffuse large B-cell Non-Hodgkin's Lymphoma	24 weeks	Yes	930	631	Yes
3	Gastric adenocarcinoma	32 weeks	Yes	239	256,000	Yes
4	Hodgkin's Disease	9 weeks	Yes	92	1,693	Yes
5	Hodgkin's Disease	55 weeks	Yes	128	244	Yes
6	Large cell Non-Hodgkin's Lymphoma	25 weeks	Yes	89	76,233	Yes
7	Perianal squamous cell carcinoma	13 weeks	No, discontinued VCV 5 weeks prior	77	57,857	No
8	Progression of Kaposi's sarcoma Plasmablastic lymphoma	150 weeks 153 weeks	Yes No, discontinued VCV 26 weeks prior	261 341	<50 <50	No No
9	Progression of Kaposi's sarcoma	24 weeks	No, discontinued VCV 26 weeks prior	6	33,582	No
10	Squamous cell carcinoma Metastatic squamous cell carcinoma of unknown origin	0 120 weeks	No Yes	180 221	44327 114	No No
11	Squamous cell carcinoma in situ (abdominal skin)	91 weeks	Yes	54	534	No
12	Vulvar squamous cell carcinoma	13 weeks	No, discontinued VCV 151 weeks prior	324	<50	No

VCV=vicriviroc