Short communication

Hepatic safety of maraviroc in patients with HIV-1 and hepatitis C and/or B virus: 144-week results from a randomized, placebo-controlled trial

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Introduction

Progressive liver disease is an important cause of morbidity and mortality in HIV-1-infected patients because of frequent coinfection with HCV and/or HBV [1–3]. Acceleration of liver disease leading to hepatic fibrosis and cirrhosis in coinfected patients may be due to continuous inflammation, which is enhanced by HIV infection [4]. Maraviroc is a potent, selective C-C chemokine receptor type-5 (CCR5) antagonist indicated for HIV-infected patients with only CCR5-tropic HIV-1 [5]. By binding to a host receptor (CCR5) rather than a viral target, maraviroc prevents interaction between HIV-1 gp120 and CCR5-tropic HIV-1, inhibiting viral

Background: In the primary 48-week analysis of a hepatic safety trial in patients with HIV-1 coinfected with HBV and/or HCV, maraviroc-containing treatment regimens were not associated with increased hepatotoxicity. Methods: In this randomized, double-blind, placebo-controlled, multicentre study, patients received maraviroc twice daily (n=70) or placebo (n=67) with concomitant antiretroviral therapy for 144 weeks (Clinicaltrials.gov identifier, NCT01327547). The primary end point was the proportion of patients with protocol-defined Grade 3/4 alanine aminotransferase (ALT) abnormalities through week 48. Key secondary end points included 144-week analysis of Grade 3/4 ALT abnormalities and liver fibrosis by enhanced liver fibrosis (ELF) testing, hepatic elastography and an optional biopsy substudy. Results: Through 144 weeks of treatment, two (maraviroc) and three (placebo) patients met the protocol-defined Grade 3/4 ALT end point. Similar to the 48-week results, there were no statistically significant differences between groups in change from baseline in ELF or hepatic elastography. However, decreased elastography scores were noted in the maraviroc group. Blinded pathologist review suggested that 2 of 11 paired biopsies (both on maraviroc) showed signs of decreased fibrosis. One (maraviroc) and two (placebo) patients experienced treatment-related hepatobiliary adverse events (AEs). Five patients in the maraviroc group discontinued because of treatment-related hepatobiliary adverse events (AEs). Five patients in the maraviroc group discontinued because of treatment-related AEs versus three in the placebo group. One death in the maraviroc group and two deaths in the placebo group were reported. Conclusions: Use of maraviroc did not increase hepatotoxicity in this population through 144 weeks. Further investigation regarding possible beneficial effects of maraviroc on liver fibrosis may be warranted.
entry [6–9]. The CCR5 co-receptor expressed on hepatic stellate receptors could also be an important therapeutic target for prevention of fibrogenesis [10]. Blockade of the CCR5 receptor may attenuate both immune and inflammatory responses and possibly reduce migration of hepatic stellate cells [10].

Previously, primary results of a randomized placebo-controlled trial assessing hepatic safety of maraviroc showed that the maraviroc-containing regimen did not increase hepatotoxicity signals in patients coinfected with HIV-1 and HCV and/or HBV through 48 weeks [11]. Herein, we report 144-week data, including exploratory end points examining fibrosis changes.

Methods

Study design and population
Detailed methods have previously been described [11]. Briefly, this 144-week, randomized, double-blind, placebo-controlled, multicentre, Phase IV study (Clinicaltrials.gov NCT01327547) included treatment-experienced adults with HIV-1 who were virologically suppressed (HIV-1 RNA <50 copies/ml) for >3 months before screening and had positive hepatitis B surface antigen (HBsAg) and/or HCV RNA results at screening. HIV-1 tropism was not required for entry into the study. Patients receiving or planning to receive anti-HCV treatment were excluded. Other key exclusion criteria included alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >5× upper limit of normal (ULN), direct bilirubin >1.5× ULN, Child–Pugh class C category (score >9) and underlying liver disease.

Patients were randomized to receive maraviroc, dose-adjusted according to their concurrent medications, or placebo, which was added to their concurrent HIV-1 suppressive antiretroviral therapy (3–6 drugs excluding low-dose ritonavir for ≥5 months before screening) for 144 weeks with a 4-week follow-up period at the end of study.

Safety and liver fibrosis assessments
The primary end point was the percentage of patients with Grade ≥3 ALT abnormalities (defined as >5× ULN for patients whose baseline ALT ≤ ULN or >3.5× baseline for patients whose baseline ALT > ULN) through 48 weeks, which was then further observed through 144 weeks (secondary end point) in the maraviroc versus placebo groups. Secondary end points also included evaluation of hepatotoxicity; change from baseline in hepatic elastography (only at sites with access to FibroScan® [Echosens, Paris, France]); percentage of patients with plasma HIV-1 RNA <40 copies/ml at weeks 48, 96 and 144; evaluation of immune markers; and safety and laboratory assessments. Analyses of enhanced liver fibrosis (ELF) test results, through 144 weeks of study treatment, were also performed. The ELF test is a combined measurement of three markers: hyaluronic acid, tissue inhibitor of metalloproteinase (TIMP-1) and procollagen III N-terminal peptide (PIIINP). These are components of the extracellular matrix and basement sinusoidal membrane of the liver and are elevated during activation of stellate cells. They play a key part in remodelling hepatic architecture, leading to fibrosis. Some studies have described the relationship between the changes seen in the serum levels of these markers and the severity of disease [12]. A liver biopsy substudy was performed, including staining of hepatic tissue for markers of fibrosis as well as independent blinded pathologist fibrosis scoring.

Sample size and statistical methods
Analyses were conducted using the full analysis set population (all patients taking ≥1 dose). Primary end point was analysed by comparing the proportion of patients with Grade 3 and Grade 4 ALT abnormalities through week 48 in the maraviroc and placebo groups. The Cochran-Mantel-Haenszel (CMH) approach was used to calculate the difference in the proportions adjusted for stratification variables. Secondary end points such as ELF and hepatic elastography were analysed using an analysis of covariance (ANCOVA) model with change from baseline as the response variable; treatment group as the main effect; and HBV status, protease inhibitor-based regimen, and baseline measurement as covariates. Least squares (LS) means and 95% CIs were reported. Missing values were imputed according to the last observation carried forward (LOCF) approach for all analyses.

Results

Patient disposition and baseline demographic characteristics
Of 218 patients screened, 137 were randomized and received ≥1 dose of maraviroc twice daily (n=70) or placebo (n=67; Table 1). All subjects who received >1 dose of study drug were included in the full analysis set for analysis and reporting of results. Twenty-six maraviroc-treated patients (37.1%) and 21 placebo-treated patients (31.3%) were discontinued from study treatment before study completion at week 144 (Additional file 1). Mean duration of HIV-1 infection was 14.9 years (range 0.9–32.1). Baseline demographics were previously reported in the published week 48 manuscript [11].

Safety
One patient each in the maraviroc (1.4%) and placebo (1.5%) groups experienced a Grade ≥3 ALT abnormality primary end point through 48 weeks [11]. By week
Hepatic safety of maraviroc in patients with HIV-1 and HBV and/or HCV

Table 1. Demographic and baseline characteristics

|                        | Maraviroc (n=70) | Placebo (n=67) | Total (n=137) |
|------------------------|------------------|----------------|---------------|
| Mean age, years (SD; range) | 47.9 (9.0; 28–75) | 48.7 (7.2; 33–62) | 48.3 (8.1; 28–75) |
| Male, n (%)            | 60 (85.7)        | 57 (85.1)      | 117 (85.4)    |
| Race                   |                  |                |               |
| White, n (%)           | 53 (75.7)        | 56 (83.6)      | 109 (79.6)    |
| Black, n (%)           | 14 (20.0)        | 10 (14.9)      | 24 (17.5)     |
| Other, n (%)           | 3 (4.3)          | 1 (1.5)        | 4 (2.9)       |
| Coinfection status     |                  |                |               |
| HBV coinfection, n (%) | 22 (31.4)        | 22 (32.8)      | 44 (32.1)     |
| HCV coinfection, n (%) | 47 (67.1)        | 47 (70.1)      | 94 (68.6)     |
| Baseline total bilirubin |                 |                |               |
| Normal, n (%)          | 66 (94.3)        | 65 (97.0)      | 131 (95.6)    |
| Grade 1, n (%)         | 4 (5.7)          | 2 (3.0)        | 6 (4.4)       |
| Baseline AST           |                  |                |               |
| Normal, n (%)          | 58 (82.9)        | 50 (74.6)      | 108 (78.8)    |
| Grade 1, n (%)         | 11 (15.7)        | 14 (20.9)      | 25 (18.2)     |
| Grade 2, n (%)         | 1 (1.4)          | 2 (3.0)        | 3 (2.2)       |
| Grade 3, n (%)         | 0                | 1 (1.5)        | 1 (0.7)       |
| Baseline ALT           |                  |                |               |
| Normal, n (%)          | 51 (72.9)        | 49 (73.1)      | 100 (73.0)    |
| Grade 1, n (%)         | 16 (22.9)        | 14 (20.9)      | 30 (21.9)     |
| Grade 2, n (%)         | 3 (4.3)          | 3 (4.5)        | 6 (4.4)       |
| Grade 3, n (%)         | 0                | 1 (1.5)        | 1 (0.7)       |
| Baseline concomitant protease inhibitor, n (%) | 33 (47.1) | 30 (44.8) | 63 (46.0) |

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1No Asian patients were included in this study. 2HBV and HCV coinfection defined as positive HBV surface antigen and HCV RNA, respectively, at screening. 3Two patients in the placebo group were coinfected with both HBV and HCV. 4None of the patients had Grades 2–4 baseline total bilirubin or Grade 4 baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values.

144, a total of two patients (3%) in the maraviroc group (observed at days 253 and 757) and three patients (5%) in the placebo group (observed at days 64, 484 and 841) experienced Grade ≥3 ALT abnormality. Hy’s law criteria, serum total bilirubin (TBL) elevation (≥2× ULN) in patients with simultaneous aminotransferase (AT) elevations (≥3× ULN) and no other reason to explain the combination TBL and AT elevations, were not met by any patients. Protocol-defined liver stopping criteria and/or Grade 4 ALT abnormalities were met by one patient (maraviroc group) between week 48 and week 144, whose ALT increased from 37 IU/l at baseline to 486 IU/l on day 757, which the investigator attributed to an active syphilis infection accompanied by a hepatic flare that resolved with treatment.

Forty-three treatment-emergent adverse events (TEAEs) in 21 maraviroc-treated patients (30.0%) and 38 TEAEs in 20 placebo-treated patients (29.9%) were considered by the investigators to be treatment related (Table 2). The most commonly reported (n≥5) treatment-related TEAEs were associated with the nervous system (n=7; 10.0%) and gastrointestinal disorders (n=5; 7.1%) in the maraviroc group and gastrointestinal disorders in the placebo group (n=12; 17.9%). Minor laboratory changes from baseline were observed, but there was no statistically significant difference between treatment groups through week 144 for hepatic laboratory tests (Additional files 2 and 3). Discontinuation from study treatment due to treatment-related TEAEs occurred in five (7.1%) maraviroc and three (4.5%) placebo patients. Three deaths were reported (maraviroc, n=1; placebo, n=2). In the maraviroc group, a 48-year-old male died of hypoxic-ischaemic encephalopathy (secondary to recreational drug overdose) on day 548. In the placebo group, a 36-year-old male died of cardiac arrest on day 226, and a 63-year-old male died of myocardial infarction on day 580. Overall, treatment-emergent cardiac disorders were noted in three (4.3%) maraviroc and six (9.0%) placebo patients with no treatment-related cardiac disorders observed in either group. Two treatment-emergent malignancies were observed: 1 (1.4%) in the maraviroc group considered possibly related to study treatment (hepatocellular carcinoma, day 908, 19 days post last dose) and 1 (1.5%) in the placebo group considered unrelated to study treatment (hepatocellular carcinoma, day 965, 17 days post last dose) during the course of the study. After study completion, a patient lost to follow-up who had received maraviroc through day 582 informed the site that he had been diagnosed with hepatocellular carcinoma (~day 733, ~151 days post dosing). This event was considered possibly related...
to maraviroc by the investigator. The patient’s medical history included HCV (1992), prostate cancer (2011), alcohol use and intravenous drug use. This case was not included in the study database as the patient was lost to follow-up at study completion, but has been added to the safety database as a spontaneously reported event.

At week 144, mean (standard deviation [SD]) decreases from baseline in hepatic elastography of -1.7 kPa (2.45) and -0.3 kPa (4.39) were observed with maraviroc (n=25) and placebo (n=28), respectively. However, the difference between groups was not significant based on subsequent ANCOVA analysis (P=0.1366). The LS mean change (standard error [SE]) in ELF from baseline was not statistically significant. Additionally, there was no statistically significant difference between treatment groups in change from baseline in markers of immune activation.

**Discussion**

These data show that 144-week use of maraviroc-containing regimens did not increase hepatotoxicity in the study population compared with placebo. The relatively lower-than-expected hepatotoxicity in patients coinfected with HIV-1 and HCV and/or HBV in this study could be explained by patients receiving virologically suppressive antiretroviral therapy, as well as the exclusion of patients with underlying liver disease. This is consistent with prior evidence that the risk of hepatotoxicity related to recently approved antiretroviral therapies is low but worsens with the presence of underlying chronic HCV [13].

Several cytokines and chemokines in response to inflammation may lead to activation, proliferation and migration of hepatic stellate cells, which play a key role in liver fibrogenesis via stimulation of CCR5 receptors [10]. Therefore, this study also explored the potential anti-fibrotic activity of maraviroc. The blinded pathologist observed a decrease in fibrosis in two of six maraviroc-treated biopsy substudy patients. Additionally, hepatic

| Table 2. Adverse event summary* |
|---------------------------------|
|                                |
| All-causality AEs              |
| Maraviroc (n=70) | Placebo (n=67) | Maraviroc (n=70) | Placebo (n=67) |
| Number of AEs                  | 452           | 545             | 43             | 38             |
| Patients with AEs, n (%)       | 64 (91.4)     | 63 (94.0)       | 21 (30.0)      | 20 (29.9)      |
| Hepatobiliary AEs, n (%)       | 2 (2.9)       | 7 (10.4)        | 1 (1.4)        | 2 (3.0)        |
| DAIDS Grade 3 or 4 AEs, n (%)  | 28 (40.0)     | 21 (31.3)       | 5 (7.1)a       | 1 (1.5)a       |
| SAEs, n (%)                    | 22 (31.4)     | 19 (28.4)       | 2 (2.9)        | 1 (1.5)        |
| Hepatobiliary SAEs, n (%)      | 1 (1.4)       | 1 (1.5)         | 0              | 0              |
| Category C AIDS-defining illness, n (%) | 1 (1.4) | 2 (3.0) | 0              | 0              |
| Malignancy, n (%)              | 1 (1.4)       | 1 (1.5)         | 1 (1.4)        | 0              |
| Discontinuations due to AEs, n (%) | 11 (15.7) | 4 (6.0) | 5 (7.1)        | 3 (4.5)        |
| Mortality, n (%)               | 1 (1.4)       | 2 (3.0)         | 0              | 0              |

*Individual patients may have had more than one adverse event (AE) in a given category but were counted only once for n (%) data. 'One patient was hospitalized because of cholangitis with hypertransaminasaemia and one patient had liver disorder reported as 'hepatopathy due to interruption of tenofovir'. Includes cholestasis (n=1), chronic cholecystitis (n=1), hepatic pain [reported as ‘liver pain on palpation’; n=1], hepatic steatosis (n=2), hepatomegaly (n=2), hyperbilirubinemia (n=1).

**Efficacy**

Through week 144, 58.6% (n=41) of maraviroc and 67.2% (n=45) of placebo patients maintained viral suppression (<40 copies/ml), each in combination with cART. At week 144, HIV-1 RNA >40 copies/ml were detected in five (7.1%) and three (4.5%) patients in the maraviroc and placebo groups, respectively. Among patients (n=9) with confirmed viral breakthrough and HIV-1 RNA >500 copies/ml, no tropism changes were observed. At week 144, LS mean (SE) increase in CD4+ T-cell levels from baseline was observed with both maraviroc (19.17 cells/µl [23.47]; P<0.3859) and placebo (46.87 cells/µl [23.47]; P=0.8087; Figure 1).

Eleven patients (maraviroc, n=6; placebo, n=5) had paired baseline and week 144 biopsies. Samples from 9 patients (maraviroc, n=5; placebo, n=4) were adequate for Ishak fibrosis scoring (secondary end point). Median change from baseline in each treatment group was 0%. Evaluation of all scoring methods used from the pathologist (blinded to treatment) suggested that 2 (both in the maraviroc group) of the 11 paired biopsies showed signs of decreased fibrosis.
elastography results suggested a trend toward reduction in fibrosis associated with maraviroc treatment. However, this limited sample was not sufficient to yield statistically significant differences in change from baseline in hepatic elastography or ELF between treatment groups. Previous research has shown that chemokine receptor inhibition (in particular inhibition of CCR5) can reduce liver injury [14], suggesting a mechanism for slowing fibrosis progression by maraviroc in HIV and HBV- or HCV-coinfected patients. It is also significant to note that this study enrolled patients whose HIV infection was being adequately treated, and consequently, progression of liver fibrosis was probably slowed. This suggests that a longer observation period may be necessary to detect
any changes in fibrosis. Although no direct conclusions can be made on the basis of the limited liver biopsy data, elastography results, and study population, further evaluation of maraviroc and changes in liver fibrosis are warranted. Further evaluation is also supported by a recent retrospective study of coinfected HIV-1–HCV patients with some degree of fibrosis who were receiving maraviroc as part of cART where fibrosis, as measured by non-invasive serum markers, showed some improvement in long-term maraviroc treatment in a proportion of patients [15]. Efficacy data through week 144 showed no clinically significant difference in the maintenance of viral suppression between the maraviroc and placebo groups, and no tropism changes were observed in patients with confirmed viral breakthrough and HIV-1 RNA >500 copies/ml.

In conclusion, the potential for hepatotoxicity with maraviroc has been previously studied. The results reported here are consistent with the findings from the week 48 analysis as well as a previous study by Ayoub et al. [16] that investigated the hepatic safety of maraviroc across Pfizer-sponsored Phase I through III clinical trials. These data, together with data from clinical studies of the CCR5 antagonist vicriviroc, which showed no evidence of hepatotoxicity through 48 weeks of therapy, support our results that there is not a class effect among CCR5 antagonists [17,18]. Furthermore, hepatotoxicity associated with the CCR5 antagonist aplaviroc that led to its discontinuation was considered likely to be unrelated to the mechanism of action (that is, CCR5 inhibition) but rather due to the properties of the molecule itself [19].

The data reported here further support the conclusion that maraviroc does not increase hepatotoxicity in HIV-1-infected patients coinfected with HCV and/or HBV and is generally well tolerated. Several clinical trials are currently testing chemokine inhibition in subjects with liver inflammation and fibrosis [20] and further study may be warranted to explore the potential antifibrotic activity of maraviroc.

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Disclosure statement

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Additional files

Additional file 1: Figure of patient disposition through week 144 can be found at https://www.intmedpress.com/uploads/documents/3918_Rockstroh_Add_file_1.pdf

Additional file 2: Figure of change from baseline in total bilirubin, direct bilirubin, indirect bilirubin, AST, and ALT through week 144 can be found at https://www.intmedpress.com/uploads/documents/3918_Rockstroh_Add_file_2.pdf
Additional file 3: Table of shift summary results for laboratory results by maximum on-study DAIDS grade through week 144 can be found at https://www.intmedpress.com/uploads/documents/3918_Rockstroh_Add_file_3.pdf

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