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Grazoprevir/elbasvir for the immediate treatment of recently acquired hepatitis C virus genotype 1 or 4 infection in men having sex with men

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Running Title: GZR/ EBR for acute HCV infection

SYNOPSIS

Background: Men having sex with men (MSM) belong to the most at-high risk populations that fuel the epidemic of recently acquired hepatitis C in Europe. Alternative associations of direct antiviral agents against hepatitis C virus (HCV) need to be assessed.

Patients and methods. In this pilot trial, MSM with recently acquired genotype 1-4 HCV infection were prospectively included and received 8 weeks of oral grazoprevir 100 mg and elbasvir 50 mg in a fixed-dose combination administered once daily. The primary endpoint was sustained virological response evaluated 12 weeks after end of treatment (SVR12). Secondary endpoints were the virological characterization of failures, the quality of life before, during and after treatment and the rate of reinfection.

Results. In a 15 months period 30 patients were enrolled, all of whom were men who have sex with men. Of the 29 patients completing follow-up, 28 (96%, 95%CI=82-99%) achieved SVR12. One patient interrupted follow-up (suicide) but had undetectable plasma HCV-RNA at the end of treatment. One patient with suboptimal adherence confirmed by plasma drug monitoring relapsed and developed NS3, NS5A and NS5B RASs at positions V36M, M28V, and S556G. The most common adverse events related to study drug were diarrhoea (*n*=4, 13%), insomnia (*n*=2, 7%), and fatigue (*n*=2, 7%), although no patient discontinued treatment. No HIV-RNA breakthrough was reported in the 28 patients with HIV co-infection. At week 48, reinfection was diagnosed in 3 patients.

Conclusions. Our data support the use of grazoprevir/elbasvir for immediate treatment against HCV in order to reduce HCV transmission in MSM.

INTRODUCTION

With the use of direct-acting antivirals (DAAs), clearance of hepatitis C virus (HCV) can be achieved with short-course treatment for all HCV-infected individuals.[1] This success has prompted the World Health Organization to target HCV elimination by 2030.[2]

In Western European countries, outbreaks of recently acquired HCV among HIV-positive MSM have begun since 1996[3] and HCV incidence has failed to decline over the past decade.[4] With the increased use of pre-exposure prophylaxis against HIV, clustering of recently acquired HCV infections has also been observed between HIV-positive and HIV-negative MSM.[5] Although most settings delay treatment for 6 months in order to assess spontaneous HCV clearance, HIV-positive MSM with recently acquired HCV infection could still be engaging in at risk activity and continue to transmit HCV.[6] Short-course DAA treatment during recently acquired HCV infection could therefore be beneficial to reduce HCV transmission. Modelling studies have indeed suggested that treating HCV early-on is an essential part of the interventions needed to curb HCV incidence and reach elimination.[7-9]

Few DAA combinations exploring diverse durations of treatment, mostly involving the NS5B inhibitor sofosbuvir, have been studied for individuals with acute HCV infection. In two one-arm, open label trials, sustained virological response 12 weeks after treatment (SVR12) was achieved with 6- or 8-week sofosbuvir/ledipasvir in 77% and 100% of HCV genotype 1-4 HIV-positive individuals.[10, 11] In the SWIFT-C trial, a 12-week sofosbuvir/ribavririn regimen led to 59% with SVR12, which is clearly sub-optimal.[12] An 8-week course of he non-sofosbuvir based DAA regimen, paritaprevir/ritonavir/ombitasvir/dasabuvir±ribavirin, was examined in acute HCV genotype 1 infection, resulting in 97% with SVR12.[13] These trials were limited in that patients with acute or early chronic HCV infection were combined.

Grazoprevir and elbasvir are potent NS3/4 and NS5A inhibitors for the treatment of chronic HCV genotype 1/4 infection and have resulted in high proportions of SVR12.[14, 15] SVR12 of 96%-99% after 12-week grazoprevir/elbasvir have also been observed among HIV and chronic HCV co-infected patients harbouring HCV genotypes 1, 4 and 6 in both clinical trials[16, 17] and real-life settings.[18] Only one trial has evaluated the efficacy of this combination in individuals recently infected with hepatitis C genotype 1 or 4 in the Netherlands and after a shorter 8-week duration of treatment, reported an SVR12 of 99%.[19] Further confirmation of these results are needed. We present herein the results of a clinical pilot trial conducted in France that included MSM with a recently acquired HCV genotype 1 or 4 infection undergoing eight-week grazoprevir/elbasvir.

PATIENTS AND METHODS

Study design

The SAHIV study is an open-label, single-arm, interventional, pilot trial evaluating the efficacy and safety of 8-week grazoprevir 100 mg and elbasvir 50 mg for the treatment of recently acquired genotype 1 or 4 HCV infection. Recruitment of study participants occurred at 6 university hospitals in France (Paris – Hôpital Saint-Antoine, Hôpital La Pitié-Salpêtrière, Hôpital Bichat, Hôpital Tenon; Lyon – Hôpital de la Croix-Rousse, Lyon; Nice – CHU de Nice). The protocol was approved in accordance with the Helsinki Declaration. The trial was registered at clinicaltrials.gov (identifier: NCT02886624).

Participants

Inclusion criteria were: age ≥18 years, recently acquired HCV genotype 1 or 4 infection (defined in the Supplementary methods), plasma HCV-RNA ≥1000 IU/mL, body weight 40-125 kg, and health

coverage under the French national health system. If HIV-positive, infection had to be confirmed with a positive western blot. HIV-positive individuals were allowed to either follow an ART combination not contraindicated with grazoprevir and elbasvir or remain untreated with ART while taking the study drug. All patients signed written informed consent prior to participating in the trial.

Non-inclusion criteria were: active or recent (<6 months) opportunistic infection; primary HIV infection; hepatitis B surface antigen-positive without treatment containing a third-generation nucleoside/nucleotide analogue [tenofovir, tenofovir alafenamide, entecavir] within 2 weeks of participating; confirmed cirrhosis prior to acute HCV diagnosis; any other known causes of acute hepatitis; pregnant or breast-feeding; liver transplant recipient; progressive malignancy; history of non-adherence; participation in another clinical trial with experimental treatment; under legal guardianship or incarcerated; haemoglobin <10 g/dL (female) or <11 g/dL (male); platelet count <50,000/mm^3; neutrophil count < 750/mm^3; or contraindication to grazoprevir and/or elbasvir or to any of the excipients.

Study procedures

Participants received an oral, fixed-dose, once-daily combination of grazoprevir (100 mg) and elbasvir (50 mg) for eight weeks. HCV genotype and HCV-RNA viral load were obtained either at screening visit or from a previous biological test performed 1-4 weeks before treatment initiation. RAS testing was not performed prior to treatment initiation.

After treatment initiation, patients were followed at week 4 (W4) and week 8 (W8) and post-treatment at week 4 (PTW4) and week 12 (PTW12). Blood samples were drawn at each visit to assess ALT, AST, total and conjugated bilirubin, γ-glutamyl transferase, alkaline phosphatase, full blood and platelet count, and creatinine levels. HCV-RNA viral load was measured using a commercially-

138 available PCR assay at the study centre (TaqMan 2.0 Assay Roche diagnostic or Abbott Realtime;
139 lower limit of detection: 15 IU/mL and 12 IU/mL, respectively). Genotyping was performed using
140 Versant® HCV Genotype 2.0 Assay (LiPA) (Siemens Healthcare Diagnostics Inc., Tarrytown, USA). For
141 HIV-positive individuals, HIV-RNA viral load was measured using a commercially-available PCR assay.
142 Patients were asked to fill in questionnaires on adherence at W4 and W8 and on quality of life [using
143 the Short Form (SF)-12v2] at treatment initiation and PTW12.

144

145 If SVR12 was not achieved, drug concentrations were quantified on stored plasma samples obtained
146 during treatment (W4 and W8) using UPLC coupled with tandem MS (Acquity-TQD, Waters
147 Corporation; Milford, MA, USA).[20,21,22]

148

149 For post-treatment study visits at which HCV-RNA levels were detectable, HCV drug resistance
150 profiles were determined from stored serum samples at baseline and the study visit where failure
151 was recorded [23, 24] NS3, NS5A and NS5B sequencing analysis were performed by in-depth
152 phylogenetic analysis. The phylogenetic trees were visualized using Dendroscope (version 3.5.9) and
153 used to differentiate between late relapse of the same infection or reinfection with another HCV
154 strain. HCV-RNA testing continued until 48 weeks post-treatment to assess HCV re-infection.

155

156 **End-points**

157

158 The primary outcome was SVR12, defined by undetectable plasma HCV-RNA twelve weeks after end
159 of treatment (EOT). The secondary outcomes included virological failure at the end of follow-up, as
160 determined by the number of patients harbouring HCV (NS5A, NS5B and NS3/4) resistance
161 mutations, and reinfection. For HIV-positive individuals, the median levels of HIV-RNA and CD4+ T
162 cell count at baseline and PTW12 were also evaluated.

163

Statistical analysis

Given the single-arm, non-comparative design, the sample size calculation was based on statistical precision and not on a comparative statistical test. Assuming an absolute precision of <30% between lower and upper bounds of the Clopper-Pearson 95% CIs for a binomial end-point and an SVR12 in ITT analysis at ≥80%, a total 30 patients were necessary.

In PP analysis, all available HCV-RNA data at PTW12 were used to calculate SVR12. In ITT analysis, all available HCV-RNA data were used to calculate SVR12, yet individuals lost to follow-up prior to PTW12 were considered as not achieving SVR12.

Scores from the SF-12 were calculated for each of the eight quality of life domains. All scores were transformed to range from 0 to 1 with higher scores indicating better mental or physical health. Scores were compared between treatment initiation and PTW12 using a fractional probit model with cluster-adjusted variance estimators.

Statistical analysis was conducted using STATA v15.0 (College Station, TX, USA). Significance was determined using a *p*-value <0.05.

Role of funding source

This was an investigator-initiated study funded by Merck Sharp & Dohme Corp. The funding source was not involved in any part of data collection, interpretation of data or writing of the manuscript.

RESULTS

Description of the study population

Between 31 May 2017 and 20 August 2018, of 33 individuals assessed for eligibility, 3 did not meet inclusion criteria (Figure 1). Thirty individuals were allocated to study treatment, all of whom received eight-week grazoprevir/elbasvir. The distribution of criteria sets used to define acute HCV infection at inclusion is provided in Table S1.

Patient characteristics at grazoprevir/elbasvir initiation are described in Table 1. Median time between suspected presentation of acute HCV symptoms and treatment initiation was 85 days (IQR=63-130). Illicit drug use over the past 12 months was found in 18 (75%) patients (Table S2). Ten patients (33%) were diagnosed as re-infected, either by change in HCV genotype from previous known infection (*n*=4) or positive HCV-RNA viral load from previously successful treatment (*n*=6). Eight (27%) patients had an STI within 12 months prior to inclusion, with the most common STIs being *Neisseria gonorrhoea* (5 infections) and syphilis (4 infections).

Median HCV-RNA was 5.71 $\log_{10}$ IU/mL (IQR=5.08-6.44) and patients harboured genotype 1a (*n*=15), genotype 1b (*n*=1) or genotype 4 (*n*=14). Of note, 8 patients had an HCV-RNA viral load >800,000 IU/mL and genotype 1a. Median ALT and AST levels were 282 IU/L (IQR=100-202) and 128 IU/L (IQR=100-202), respectively, and 3 (10%) presented with ALT or AST levels ≤2x upper limit of normal.

The large majority of patients were HIV-positive (*n*=28), all of whom were undergoing ART with either undetectable HIV-RNA (n=26, <40 copies/mL) or low-level replication (n=2, at 51 and 90 copies/mL). No patient was on an agent having possible drug interactions with study medication. Immunosuppression was largely mild with only 3 (11%) HIV-positive patients having a previous AIDS-defining illness and median CD4+ cell count at 580/mm^3 (IQR=467-706).

Virological and biochemical response

Of the 30 included patients, all completed 8 weeks of grazoprevir/elbasvir. During post-treatment follow-up, one patient died (suicide occurring 3 weeks after the W8 visit). In total, 29 completed the PTW12 visit. The proportion of detectable HCV-RNA at each follow-up visit is given for both PP and ITT analysis in Figure 2A. The proportion of patients achieving SVR12 was 93% (95%CI=78-99%) in ITT analysis and 96% (95%CI=82-99%) in PP analysis. SVR12 was not different between individuals with or without re-infection (*n*=10/10, 100% and *n*=18/19, 95%; respectively) or between individuals with baseline HCV-RNA ≤800,000 IU/mL or >800,000 IU/mL (*n*=16/16, 100% and *n*=12/13, 92%; respectively).

As shown in Figure 2B, most patients were able to normalize transaminase levels at the PTW12 visit. One patient had increasing ALT levels from 78 IU/L at baseline to 109 IU/L PTW4, then decreasing to 37 IU/L at PTW12. This patient had undetectable HCV-RNA at all visits during and post-treatment. Two patients had ALT levels >40 IU/L at their PTW12 visit: one with undetectable HCV-RNA at all visits after W4 and the other failing treatment (described below). No patient had a flare in ALT or AST >250 IU/L during or post-treatment.

One patient with GT1a experienced virological failure. Virological and biological evolution of this patient is described in Figure 3. At W4, both plasma GZR and EBR concentrations were undetectable (<5 ng/mL) and concomitant plasma antiretroviral concentrations were low (FTC, 111 ng/mL; TDF, 48 ng/mL; RPV 78 ng/mL). At W8, plasma concentrations of study drug were normal (GZR, 144 ng/mL; EBR, 105 ng/mL) including those of the antiretroviral regimen (FTC, 1074 ng/mL; TDF, 213 ng/mL; RPV, 90 ng/mL). HCV-RNA level was undetectable at PTW4 but rebounded to 6.57 $\log_{10}$ IU/mL at PTW12. Phylogenetic analysis indicated the same HCV viral strain compared to baseline, ruling out HCV re-infection. Genotypic resistance analysis at PTW12 revealed the V36M amino acid substitution in NS3, M28V in NS5A, and S556G in NS5B regions of the HCV genome.

Self-reported adherence and quality of life

At the W4 and W8 visits, respectively, 1 (4%) and 2 (7%) patients declared missing grazoprevir/elbasvir within the last 4 days and 2 (7%) and 1 (3%) forgot to take grazoprevir/elbasvir at least once during the weekend. The level of grazoprevir/elbasvir adherence was comparable to that of ART, for which 4 (15%) and 3 (11%) patients reported missing ≥1 pills included in their regimen within the last 4 days and 1 (3%) and 1 (3%) forgetting to take their medication at least once during the weekend at the W4 and W8 visits, respectively.

Based on scores from the SF-12 (Table S3), significant improvement between treatment initiation and PTW12 were observed in role physical (p=0.02) and role emotional (p=0.02) domains. No significant differences between treatment initiation and PTW12 were observed in the other six domains: physical functioning, bodily pain, general health, vitality, social functioning, and mental health. At baseline, when compared to the overall average SF-12 across domains in the entire study population (0.61), the only patient failing treatment had an average SF-12 of 0.58 and the two patients with completed and attempted suicide, respectively, had an average SF-12 of 0.79 and 0.40.

Control of HIV-infection during follow-up

At PTW12, all 27 HIV-positive participants with available data had HIV-RNA <50 copies/mL and median CD4+ T cell count was 655/mm^3 (IQR=488-829). After treatment with grazoprevir/elbasvir, 3 patients switched from TDF/FTC/RAL (n=2) or TDF/FTC/DTG (n=1) to TAF/FTC/elvitegravir/COBI (unrelated to HIV virological failure or toxicity). No HIV virological failure was reported during treatment or post-treatment.

Adverse events and serious adverse events

During treatment and post-treatment, 60 clinical adverse events were reported and ≥1 clinical adverse event occurred in 23 (77%) participants. Only 3 serious clinical adverse events occurred: one patient had a panic attack with underlying suicidal ideation and another patient committed suicide. None of the serious clinical adverse events was related to study treatment. All other possible and probable drug-related adverse events are listed in Table 2.

Reinfection rate

No HCV re-infections were observed within 12 weeks after EOT. However, HCV-RNA was detected in 3 patients after PTW12. One patient with previous GT1a infection acquired a GT4d strain 48 weeks after PTW12, the second patient with a previous GT4 infection acquired an HCV GT1b strain 24 weeks after PTW12, and the third patient with a previous GT1a infection acquired a GT1a strain 28 weeks after PTW12, but philogenic analysis showed that it was a different strain from baseline. In total, the reinfection rate was 3/28 (10.7/100 patient-month). All have successfully been retreated with various DAA combinations for 8 to 16 weeks.

DISCUSSION

In this multicentre pilot study of MSM with recently acquired HCV infection, we observed that 96% (28/29) were able to achieve SVR12 after an eight-week course of treatment with grazoprevir/elbasvir. This proportion was 93% (28/30) assuming those lost to follow-up did not achieve SVR at the end of follow-up. These SVR rates are comparable to chronically HCV-infected individuals undergoing the same treatment combination for 12-weeks, regardless of HIV status.[15-18] Of those completing the PTW12 visit, only one exhibited RAS associated with grazoprevir/elbasvir

294 treatment failure. These data provide strong evidence that eight-week grazoprevir/elbasvir is
295 appropriate for the treatment of acute HCV infection genotype 1 and 4, and particularly in HIV-
296 positive patients.
297
298 In chronic HCV infection, the C-WORTHY trial showed that higher SVR12 rates were achieved in
299 patients treated with 12-week versus 8-week grazoprevir/elbasvir.[17] Nevertheless, more recent
300 clinical trials evaluating 8-week grazoprevir/elbasvir have demonstrated high SVR in HCV genotype
301 1b or 4 infected patients with liver fibrosis levels at METAVIR F0-F2[25,26] or in genotype 1b when
302 plasma HCV-RNA is low.[27] Given that MSM recently acquiring HCV are unlikely to have severe liver
303 fibrosis[28], 8-week duration of grazoprevir/elbasvir could be sufficient for treating acute HCV. The
304 recent DAHHS2 trial conducted in the Netherlands demonstrated that short-term duration of
305 grazoprevir/elbasvir is possible in acutely infected individuals, reporting SVR12 of 99% in 80 patients
306 with acute HCV genotype 1 (all with genotype 1a or 4 infection after 8-week grazoprevir/elbasvir).[19]
307 Our data confirm this finding with high SVR12 in both ITT and PP analysis. Furthermore, as reported
308 by Boerekamps *et al.*, SVR12 was also able to be achieved in all patients harbouring HCV genotype
309 1a (one of the most prevalent genotypes among European MSM[3]) and all but one genotype 1a-
310 infected patient with plasma HCV-RNA >800,000 IU/mL at baseline, which is also associated with
311 virologic failure during chronic HCV infection.[29]
312
313 Of note, there were four patients with detectable plasma HCV-RNA at EOT, 3 of whom eventually
314 achieved SVR12. This phenomenon has been described in chronic HCV infected individuals enrolled in
315 registration trials of peg-IFN-free DAA containing regimens.[30] The other patient with detectable HCV-
316 RNA at EOT eventually developed virological failure with the emergence of 28V and 36M RAS, both of
317 which have been previously identified in HCV mono-infected patients with virological failure.[31] This
318 patient might not have been consistently using study medication, as indicated by the undetectable
319 plasma grazoprevir/elbasvir and ARV concentrations at W4. Emergence of these substitutions would

likely be the result of selective pressures from poor adherence and not necessarily insufficient treatment duration.

Poor quality of life has been associated with suboptimal adherence and early treatment discontinuation[32, 33], thereby increasing the risk of virologic failure. In our study, we were able to observe improvements in both role physical and role emotional domains. Studies on patient-reported outcomes during and after grazoprevir/elbasvir treatment for chronic HCV have observed improvements in many domains, including mental health and role physical, but not with role emotional.[34] Differences between studies could be the result of included study populations (acute versus chronic HCV infection) and Quality of Life inventories (SF-36 versus SF-12). Yet considering the limited data on quality of life during DAA-treated acute infection, it is difficult to explain these discrepancies any further.

Despite some improvements in quality of life, no change in the mental health domain was observed. It is also noteworthy that, after EOT, one patient attempted suicide and another committed suicide. Illicit drug use within the 12 months prior to baseline was observed in 75% of patients with available data. Half of these individuals had consumed drugs that are known to be associated with high risk sexual behaviour and STI acquisition[35] and whose use could be potentially driven by internalizing mental health disorders.[36] These observations underscore the need to incorporate mental health and addiction services when treating HCV in this key population.

The proportion with a probable or possible drug-related adverse event was low and in line with previous studies using grazoprevir/elbasvir in HCV mono-infection or HIV/HCV co-infected populations.[15,18,19] Besides the serious mental health problems identified during follow-up, no other serious adverse events and no serious laboratory abnormalities were observed. Other studies have included STIs as a part of adverse events, reported in roughly 24% of MSM twelve weeks after

grazoprevir/elbasvir treatment.[19] We did not consider this as an adverse event; nevertheless, 27% of included patients reported at least one bacterial STI within the year prior to treatment initiation and among them, 88% reported having at least one adverse event during follow-up. Assuming that STIs were only to occur in patients with previously detected infections, the proportion with adverse events during treatment would not have changed.

In HIV-positive individuals, potential drug-drug interactions between grazoprevir/elbasvir and certain antiretroviral agents are problematic and reconsideration of ART regimen might be required for a number of patients planning to initiate grazoprevir/elbasvir.[37] ART regimens had to be modified in only one of the twenty-eight HIV-positive individuals without concern and no rebounds in plasma HIV-RNA or changes in CD4+ T cell count were observed in ART-experienced patients during grazoprevir/elbasvir treatment.

There are certain limitations to our study. First, treatment efficacy was not assessed using a non-inferior study design. Nevertheless, we argue that any non-inferiority limit assuming an SVR12 rate below 90% would be uninstructive given the efficacy of current DAA treatments. Second, we included a limited number of acute HCV infected individuals, reducing the potential numbers of virological failures and hence our ability to determine reasons for failure. There were also few HIV-negative participants enrolled, which limits generalizability to this group. Finally, data on baseline RAS were not collected and thus we cannot conclude on the efficacy of grazoprevir/elbasvir in the presence of these substitutions. NS5A RAS appear to mostly affect virologic response in patients with high HCV viral loads[27] or those infected with HCV genotype 1a and less so with genotype 1b or 4.[15,38-40] Half of included patients were infected with genotype 1a, which would make data on RAS particularly helpful. Nevertheless, in the DAHHS2 study, where sequencing was performed at baseline for all patients, no one harbouring a strain with RAS experienced virological failure.[19]

In conclusion, given the 96% SVR12 rate and the single patient with RAS, eight-week grazoprevir/elbasvir is an efficacious treatment option for recently acquired HCV infection. As adverse events were uncommon, particularly those related to the study drug, this treatment would appear well-tolerated. These data support the use of grazoprevir/elbasvir for rapid treatment against HCV, appropriate for reducing ongoing HCV transmission in the current epidemic of HCV infection among European MSM with genotypes 1 and 4. The suicide attempt and completed suicide coupled with frequent illicit drugs use observed in this study population stress the need for mental health services in MSM at risk for HCV infection.

ACKNOWLEDGEMENTS

We are grateful to the patients and clinical teams involved in the SAHIV Study.

The SAHIV clinical study team: Hôpital Saint-Antoine – Julie Bottero, Jessica Krause, Michel Pauchard, Julie Lamarque; Hôpital Tenon – Julie Chas, Anne Adda; Hôpital La Pitié-Salpêtrière – Marc-Antoine Valantin, Ludovic Lenclume; Hôpital Bichat – Yazdan Yazdanpanah, Malikhone Chansombat; CHU de Lyon – Patrick Miailhes, Valérie Galvan; CHU de Nice – Eric Rosenthal, Sophie Bréaud. Coordinating pharmacy: Hôpital Saint-Antoine – Anne Daguenel-Nguyen. Data management team: Inserm U1136 – F. Chau, G. Mawuvi, M. Angot, F. Carrat.

Scientific advisory board: Karine Lacombe, Pierre-Marie Girard, Jessica Krause, Julie Chas, Marc-Antoine Valantin, Yasdan Yazdanpanah, Patrick Miailhes, Eric Rosenthal, Stéphane Chevaliez, Lionel Piroth, Amir Guidoum, Anders Boyd, Hayette Rougier.

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FUNDING

MSD provided an unrestricted grant for the study and was not involved in any part of the data collection, analysis, and writing.

TRANSPARENCY DECLARATIONS

KL reports receiving travel grants and advisory board fees from Gilead, Abbvie and MSD.

SC reports receiving advisory board fees from Abbott and Cepheid.

All other authors: none to declare

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529 **TABLES**

530

531 **Table 1. Description of the study population at treatment initiation**

532

General characteristics	***N*=30**
Male gender*	30 (100)
Birth country/region*	
France	22 (73)
Europe (outside of France)	3 (10)
Asia	3 (10)
Other	2 (7)
Age, years[†]	44 (34-52)
BMI, kg/m^{2}[†]	22.4 (20.6-25.4)
Hypertension*[‡]	10 (33)
Diabetes*[§]	1 (3)
Co-infection with HIV*	28 (93)
HCV-related characteristics	***N*=30**
Transmission route*[¶]	
Nasal drug-use	6 (20)
Injection drug-use	5 (17)
Sexual contact	23 (77)
Unknown	2 (7)
Involved first HCV reinfection*	9 (30)
Involved second HCV reinfection*	1 (10)
Time since last infection, years[†]	2.8 (1.2-3.8)

533

Table 1 (con't).

HIV-related characteristics	***N*=28**
Known duration of HIV infection[†]	8.5 (4.5-14.0)
AIDS-defining illness*	3 (11)
Undergoing ART**µ	28 (100)
HIV RNA viral load >50 copies/mL*	2 (7)
HIV RNA viral loads, copies/mL**	(51, 90)
CD4+ T cell count, /mm^{3}[†]	580 (467-706)
CD8+ T cell count, /mm^{3}[†]	644 (508-964)
CD4:CD8 ratio[†]	0.84 (0.55-1.24)

*_n_ (%) [†]Median (IQR)

[‡]Systolic blood pressure >130 mm/Hg or diastolic blood pressure >80 mm/Hg.

[§]Declared by treating physician.

[¶]More than one transmission route can occur within individuals.

**For individuals with HIV RNA >50 copies/mL.

µ TDF/emtricitabine (FTC)/rilpivirine (RPV), *n*=9; abacavir/lamivudine/dolutegravir (DTG), *n*=9; TDF/FTC/DTG, *n*=6; TDF/FTC/raltegravir (RAL), *n*=3; or TDF/FTC dual therapy, *n*=1. Of note, one patient switched from TDF/FTC/cobicistat (COBI)-boosted darunavir to TDF/FTC/DTG at treatment initiation (following recommendations for concomitant antiretroviral agents).

544 **Table 2. Adverse and serious adverse events during follow-up**

All clinical adverse events, *n*	60
Patients with ≥1 clinical adverse event, *n* (%)	23 (77)
Serious clinical adverse events, *n*	3
Panic attack	1
Suicidal ideation (without suicide)	1
Suicide	1
Serious drug-related clinical adverse events, *n*	0
Discontinuation due to clinical adverse events, *n* (%)	0 (0)
Deaths, *n* (%)	1 (3)
Cause of death	
Suicide	1
All possible drug-related adverse events	8
Diarrhoea	2
Abdominal distension	1
Stomach spasms	1
Myalgia	1
Xerostomia	1
Hyperhidrosis	1
Osteoarthritis of knee and hands	1
All probable drug-related adverse events	8
Insomnia	2
Diarrhea	2
Fatigue	2
Binge eating	1

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Table 2 (con't).

Dysgeusia	1
Patients with ≥1 grade 2 laboratory abnormality*, *n* (%)	12 (40)
Creatinine clearance 60-90 mL/min/1.73m²	12
Patients with ≥1 grade 3 or 4 laboratory abnormality*, *n* (%)	0 (0)

*Specifically during treatment.

FIGURE LEGENDS

Figure 1. Patient flow during the study

Figure 2. Hepatitis C virus (HCV) and alanine transaminase levels during and after treatment with grazoprevir/elbasvir

Number of patients with undetectable HCV over total number of patients are given during treatment at week 4 (W4) and week 8 (W8) as well as post-treatment at week 4 (PTW4) and week 12 (PTW12) in PP and ITT analysis (**A**). Individual (grey lines) and median (black line) ALT levels are given at each study visit in (**B**).

Figure 3. Virological and biochemical evolution of the patient with treatment failure

Hepatitis C virus (HCV)-RNA (genotype 1a) and ALT levels during treatment at week 4 (W4) and week 8 (W8) as well as post-treatment at week 4 (PTW4) and week 12 (PTW12) for the only patient with treatment failure. Antiretroviral (ARV), elbasvir (EBR) and grazoprevir (GZR) plasma levels were quantified at W4 and W8 and RASs were determined at PTW12.

Figure 1.

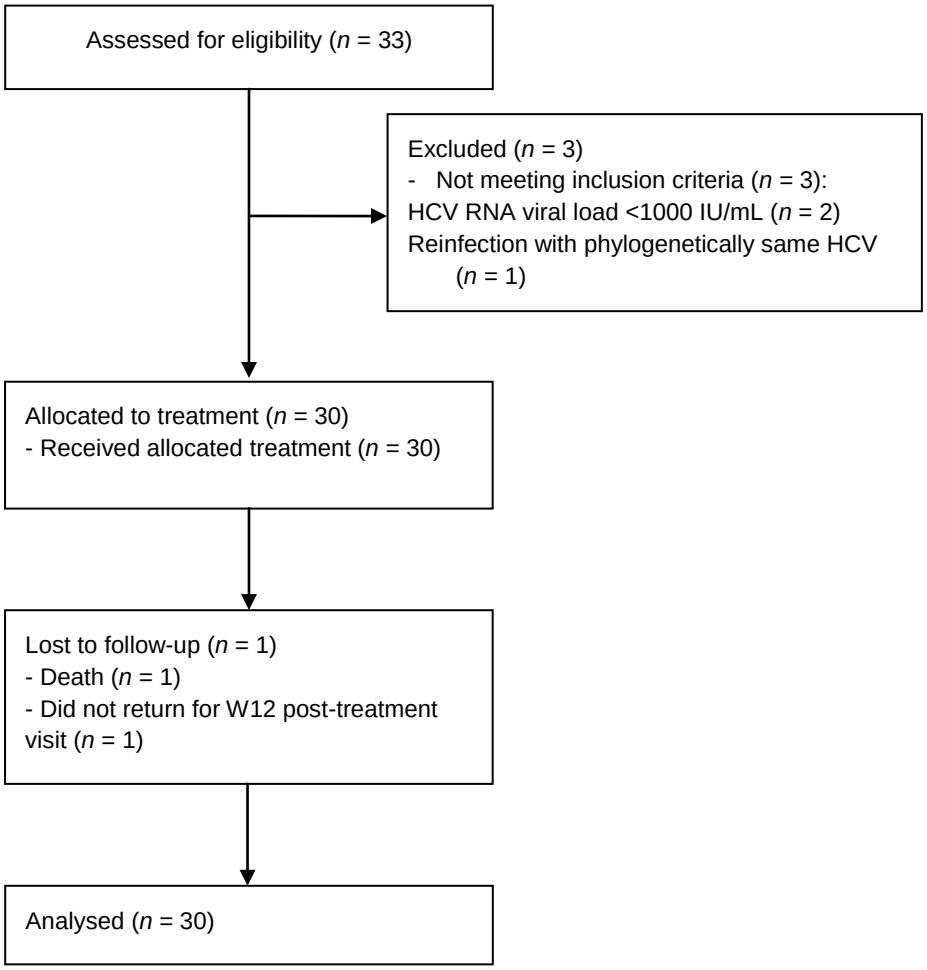
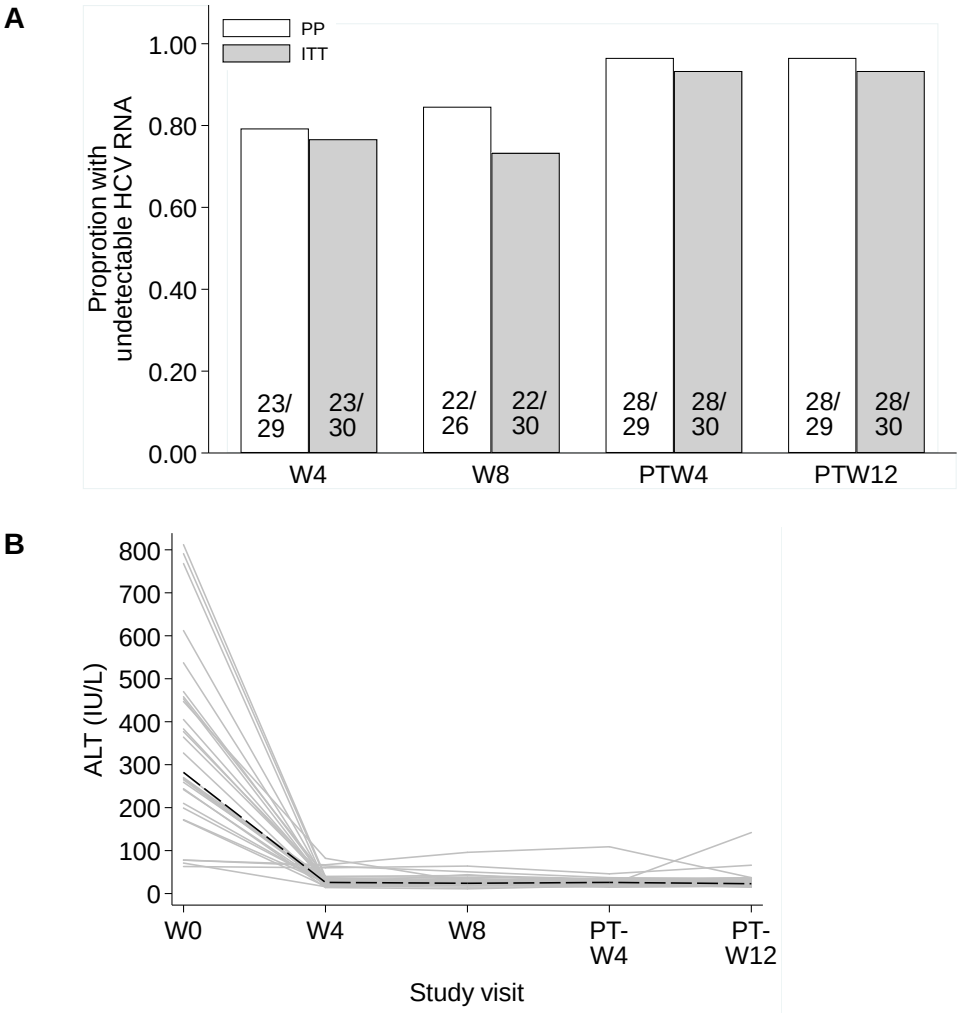
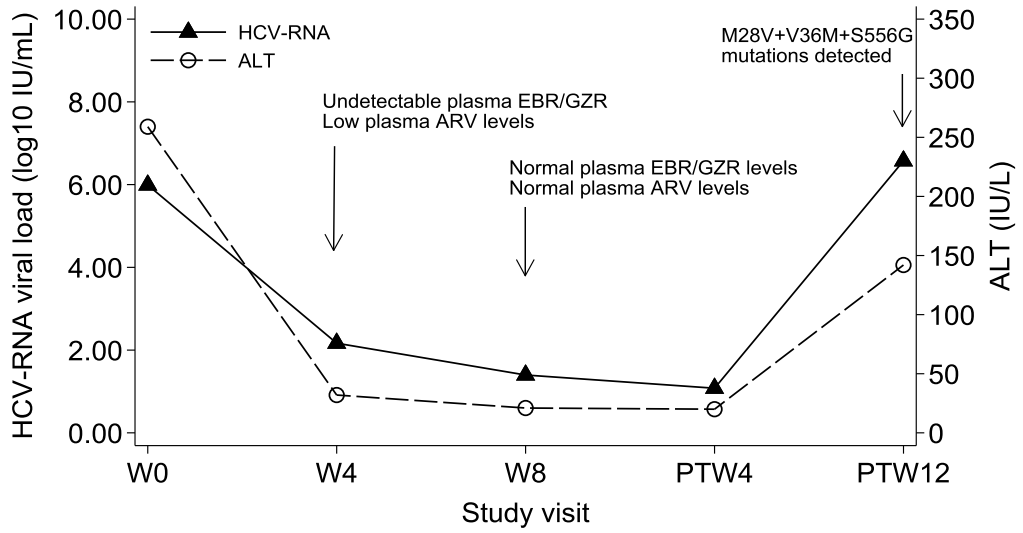

Assessed for eligibility (n = 33)
Excluded (n = 3)
- Not meeting inclusion criteria (n = 3):
HCV RNA viral load <1000 IU/mL (n = 2)
Reinfection with phylogenetically same HCV (n = 1)
Allocated to treatment (n = 30)
- Received allocated treatment (n = 30)
Lost to follow-up (n = 1)
- Death (n = 1)
- Did not return for W12 post-treatment visit (n = 1)
Analysed (n = 30)

Figure 2.


A
PP
ITT
Proprotion with undetectable HCV RNA
1.00
0.80
0.60
0.40
0.20
0.00
23/29
23/30
22/26
22/30
28/29
28/30
28/29
28/30
W4
W8
PTW4
PTW12
B
ALT (IU/L)
800
700
600
500
400
300
200
100
0
W0
W4
W8
PT-W4
PT-W12
Study visit

568 **Figure 3.**



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