Compassionate use of subcutaneously administered REP 2139-Mg in cirrhotic HBV / HDV co-infection

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Introduction

REP 2139 inhibits HDV RNA replication and HDV RNP formation via direct interaction with HDAg and HDV envelopment and release by blocking the assembly of HBV subviral particles. The safety and efficacy of SC injection of REP 2139-Mg in combination therapy is currently being assessed in cirrhotic patients with chronic HBV / HDV co-infection who fail to respond to bulevirtide (BLV).

Methods

Following washout from previous bulevirtide therapy, existing TDF therapy was supplemented with 90µg pegIFN qW and 250mg REP 2139-Mg qW via SC administration. Safety assessments included liver, kidney and hematological function. Virologic assessments included HDV RNA (Robogene MK II or EurobioPlex), HBV DNA (Abbott), HBsAg and anti-HBs (Abbott Architect quantitative).

Results

SC administration of REP 2139-Mg was well tolerated in five patients to date. Patient 1 (Senegalese male, 51, GT 5 HDV) completed 48 weeks of therapy without incident. A self-resolving transaminase flare (ALT_{max} 373 U/L at week 9) was otherwise asymptomatic. HDV RNA became undetectable at week 4 and HBsAg became undetectable with seroconversion at week 12. HDV RNA clearance was verified by pan-genotypic RT-PCR. These virological responses persisted throughout therapy. Anti-HBs titers increased to 509 mIU/mL during therapy. Two months following removal of REP 2139-Mg and pegIFN, HBsAg and HDV RNA has remained undetectable and the anti-HBs titer has increased to 983 mIU/mL.

In patients 2-5, REP 2139-Mg therapy is still ongoing with HDV RNA and HBsAg responses are evident in all patients (see below). Antiviral responses to SC REP 2139-Mg appear slower in patient 3 which is attributed to a BMI of 30. Patient 5 presented a decompensated cirrhosis (Child-Pugh B8) at baseline and was treated with REP 2139-Mg in association with TDF without pegIFN. At W4, a clear clinical improvement was observed with ascites regression and discontinuation of diuretics with no relapse.

Conclusions

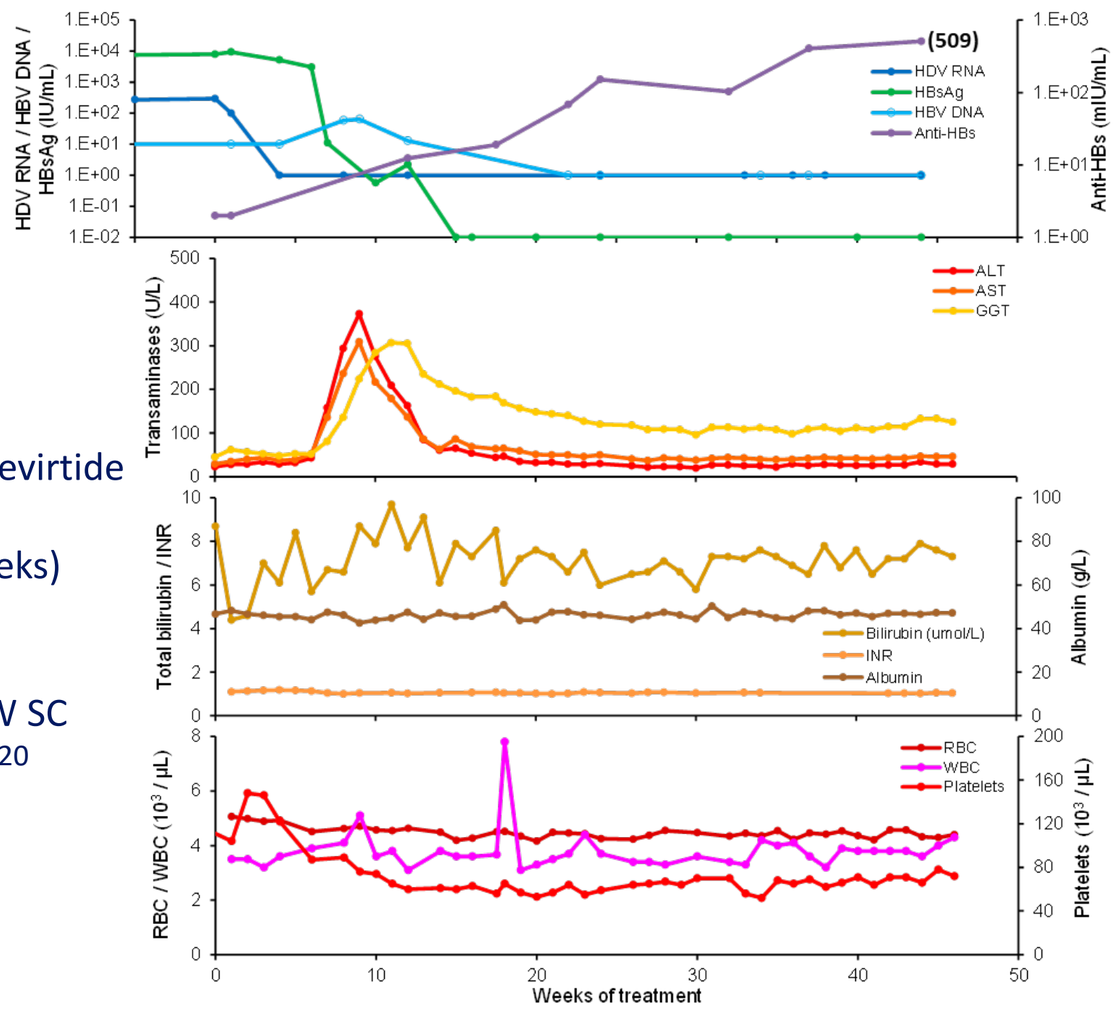
SC REP 2139-Mg is safe, well tolerated and effective against HBV and HDV infection in combination with TDF and low dose pegIFN in cirrhotic patients who failed on bulevirtide.

PATIENT 1 (Marseille)

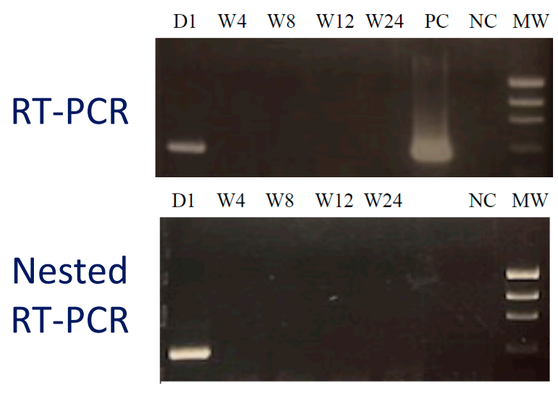
Senegalese male, 51
HBV / HDV (GT5)
Compensated cirrhosis

Previous HDV failure on:
TDF + pegIFN
TDF + pegIFN + 2mg bulevirtide

Combination regimen (48 weeks)
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC
transition to 125mg IV @ week 20



Pan-genotypic HDV RT-PCR



Removal of REP 2139-Mg and pegIFN (2 months)

HBsAg not detected (< 0.05 IU/mL)
Anti-HBs 983 mIU/mL (509 at EOT)
HDV RNA target not detected
HBV DNA target not detected

ALT 26, AST 35, GGT 84 U/L
T-BIL 6.6 µmol/L, ALB 51 g/L, INR 1.13

Platelets 129x10^3 /µL (recovering)

PATIENT 2 (Limoges)

Caucasian Male, 47
Chronic HBV/HDV infection (GT1)
Compensated cirrhosis (Child A5, stage 1 esophageal varices)

Previous HDV failure on:
TDF + pegIFN
TDF + pegIFN + bulevirtide 2mg

Combination regimen:
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC

SC administration of REP 2139-Mg well tolerated
9 weeks: HBsAg target not detected (baseline 4650 IU/mL)
13 weeks: HBsAg seroconversion 14.3 mIU/mL
22 weeks: anti-HBs 342 mIU/mL
≤ 4 weeks: HDV RNA target not detected (baseline 607,859 IU/mL)
Latest LFT: ALT 49 U/L, AST 73, GGT 141 U/L, bilirubin 9.2 µmol/L

PATIENT 3 (Clichy)

Asian Male, 54
Chronic HBV / HDV infection (GT1)
Compensated cirrhosis

Previous HDV failure on:
TDF + pegIFN
TDF + pegIFN + bulevirtide 2mg
TDF + pegIFN + bulevirtide 10mg

Combination regimen:
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC

SC administration of REP 2139-Mg well tolerated
12 weeks: HBsAg 1890 IU/mL (baseline 10285 IU/mL)
HDV RNA decline evident at week 8
Other efficacy results pending…

PATIENT 4 (Limoges)

Caucasian Female, 59
Chronic HBV/HDV infection (GT1)
Compensated cirrhosis

Previous HDV failure on:
TDF + pegIFN (hematological intolerance)
bulevirtide 2mg
bulevirtide 10mg

Combination regimen:
300mg TDF qD PO
90 µg pegIFN qW SC
250mg REP 2139-Mg qW SC

SC administration of REP 2139-Mg well tolerated
PegIFN therapy is now well tolerated
16 weeks: HBsAg 135 IU/mL (baseline 44476 IU/mL)
12 weeks: HDV RNA < LLOQ (168 IU/mL, baseline 6562 IU/mL)
Latest LFT: ALT 73 U/L, AST 67 U/L, GGT 147 U/L, bilirubin 5.4 µmol/L

PATIENT 5 (Clichy)

Caucasian Female, 54
Chronic HBV / HDV infection (GT1)
Decompensated cirrhosis (significant ascites)

Combination regimen:
300mg TDF qD PO
250mg REP 2139-Mg qW SC

SC administration of REP 2139-Mg well tolerated
Week 4: Reversal of ascites (confirmed via ultrasound)
Week 6: HBsAg 28 IU/mL (baseline 1177 IU/mL)
HDV RNA decline evident at week 8
Other efficacy results pending…