Subcutaneous administration of REP 2139-Mg in the compassionate treatment of cirrhotic HBV / HDV co-infection

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INTRODUCTION

REP 2139-Mg based combination therapy achieves high rates of HBsAg loss, therapeutic transaminase flares and functional cure of HBV and HDV when administered by weekly IV infusion[1-4]. Like all phosphorothioate oligonucleotides (antisense oligonucleotides, ASOs), subcutaneous (SC) injection site reactions[5] are common with REP 2139 but, like all NAPs, are significantly stronger because of their increased length. Chelate complex formulation of NAPs (REP 2139-Mg) neutralizes administration reactivity. The safety and efficacy of SC injection of REP 2139-Mg in combination therapy was assessed in a cirrhotic patient with chronic HBV / HDV co-infection.

METHODS

The patient (male, Senegalese, 51 years old) had confirmed cirrhosis and chronic HBV / HDV co-infection since 2005 (HDV GT3) and had failed previous therapies with TDF (300mg) + pegIFN (180ug) and later with TDF + pegIFN (180ug) + bulvertide (2mg) (Figure 1) and was currently receiving only TDF. Eight months following discontinuation of pegIFN + bulvertide, TDF therapy was supplemented with 90ug pegIFN and 250mg REP 2139-Mg given as two subcutaneous injections (SC) of 125mg once each week. The REP 2139-Mg formulation used was identical to that administered intravenously in the REP 401 study[3]. Safety assessments included liver, kidney and hematological function. Virologic assessments included HDV RNA (Robogene MK II), HBV DNA (Abbott), HBsAg and anti-HBs (Abbott Architect quantitative).

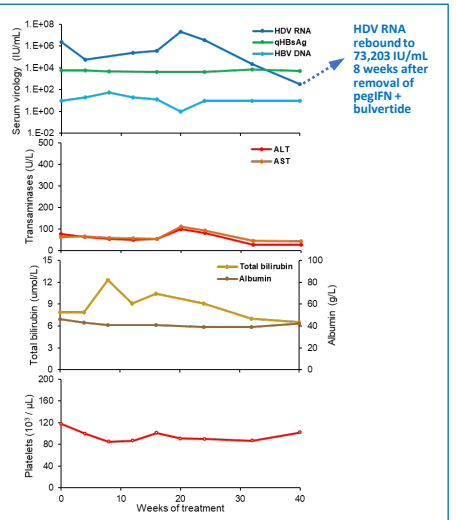

Figure 1. Virologic failure on previous therapy
Virologic, liver function and platelet response to previous therapy with TDF + pegIFN + bulvertide. Withdrawal of pegIFN and bulvertide was accompanied by HDV RNA rebound.

RESULTS

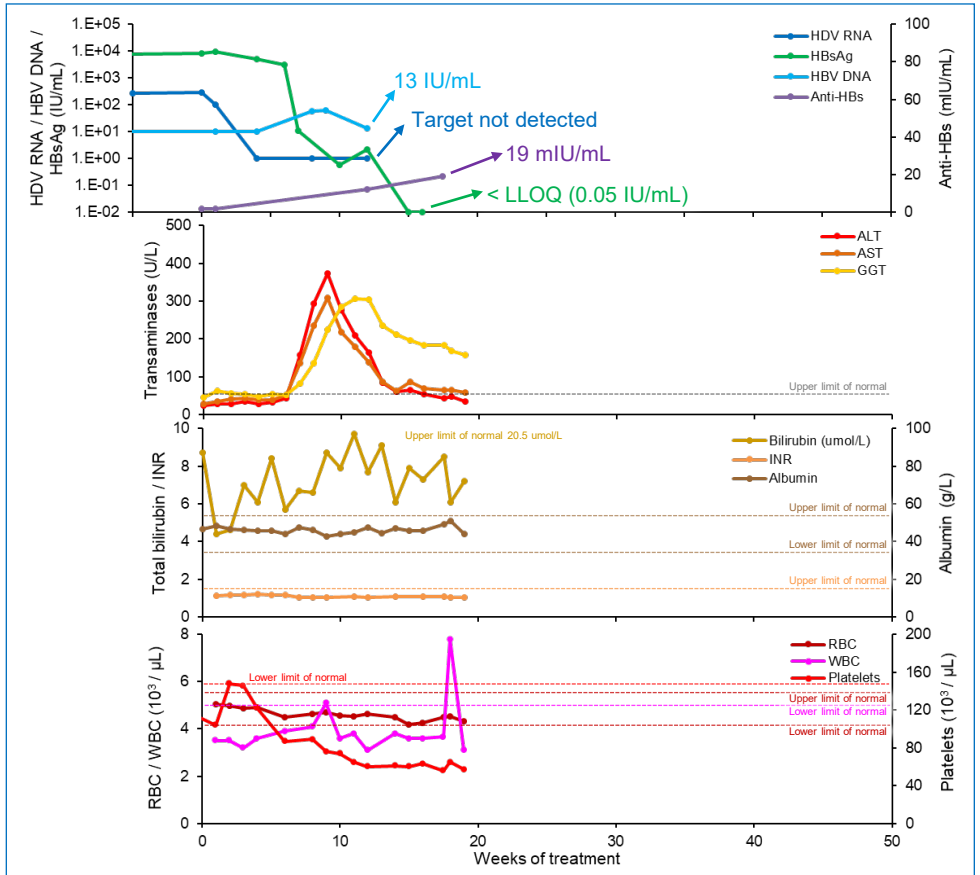

Figure 2. Response to ongoing therapy with TDF + 90ug pegIFN + 250mg SC REP 2139-Mg
Virologic, liver function and hematological response to current REP 2139-Mg based compassionate therapy.

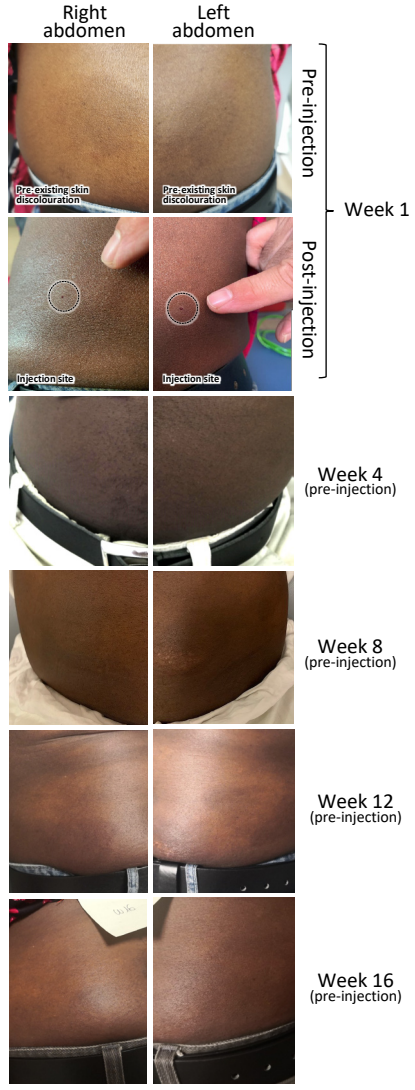

Figure 3. Injection site tolerability
Photographs of REP 2139-Mg injection sites taken at various time points during therapy.

ADVERSE EVENTS

No evidence of pain or inflammation at the injection sites for REP 2139-Mg was observed for the first 9 weeks. Thereafter, mild to moderate discomfort post injection was transient and not accompanied by inflammation. Mild pruritis after week 6 responded well to supportive therapy. Two mild and superficial indurations were not accompanied by pain or inflammation. Liver and kidney functions have remained normal throughout therapy with stable hematological parameters (RBC, WBC, platelets) in the absence of supportive therapy.

CONCLUSIONS

1. **The magnesium chelate formulation of REP 2139 effectively suppresses the normally serious injection site reactivity with NAPs.**
2. **SC REP 2139-Mg is safe and well tolerated. Injection site reactivity is minor, supporting a 48 week regimen in future clinical studies.**
3. **SC REP 2139-Mg (in combination with TDF and pegIFN) is accompanied by identical virologic responses as observed with its intravenous infusion:**
   - **Rapid HBsAg loss and seroconversion**
   - **Rapid clearance of serum HDV RNA**
   - **Host mediated transaminase flares indicating clearance of HBV infected hepatocytes from the liver.**
4. **Reduced dosing of pegIFN (90ug) appears sufficient to synergize with REP 2139 to restore immune function.**
5. **Host mediated transaminase flares were well tolerated and asymptomatic in this patient.**
6. **Activity of REP 2139 now confirmed in HDV GT1 and GT3.**

REFERENCES

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