Effects of nucleic acid polymer therapy alone or in combination with immunotherapy on the establishment of SVR in patients with chronic HBV infection.

Mamun-Al-Mahtab[1], Michel Bazinet[2] and Andrew Vaillant[2]

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Background

Nucleic acid polymers (NAPs) block HBsAg release from infected hepatocytes, a novel approach to clear serum HBsAg in human patients. Three proof of concept clinical trials examined tolerability and antiviral effects of NAPs in Asian patients with chronic, HBeAg+ HBV infection in monotherapy or in combination with immunotherapy. Follow-up data from these studies is herein reported.

Methods

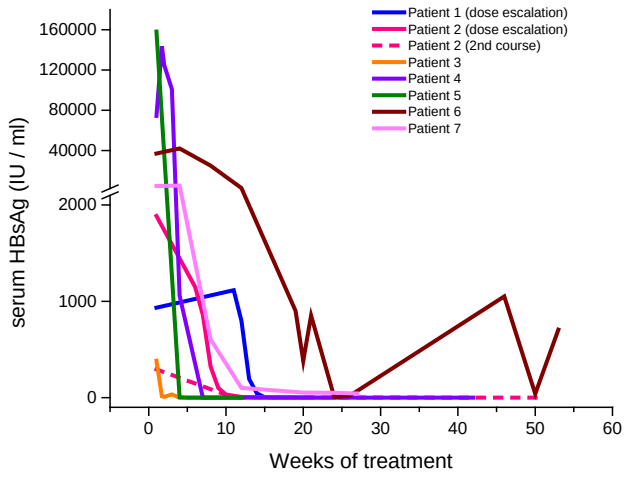
IRB approved, open label trials (REP 101, 102 and 201) were conducted in Bangladesh with no stratification or randomization. Treatment naive patients > 18 years old with chronic HBV infection (HBV DNA > 10^5 copies / ml, evidence of liver fibrosis and ALT < 5X ULN) were eligible. All patients except one were HBeAg+. NAPs were administered by intravenous infusion (400mg qW for REP 2055, 500mg qW for REP 2139-Ca). Pegasys® (180ug qW) or Zadaxin® (1.6mg 2qW) were administered by subcutaneous injection. Entecavir (ETV) was dosed orally qD (0.5mg). Primary efficacy outcomes are identified in the table below and were determined using accepted test platforms (Roche cobas®, Abbott Architect and Roche IMPACT). All patients provided informed consent before treatment.

REP 101 trial
REP 2055 monotherapy

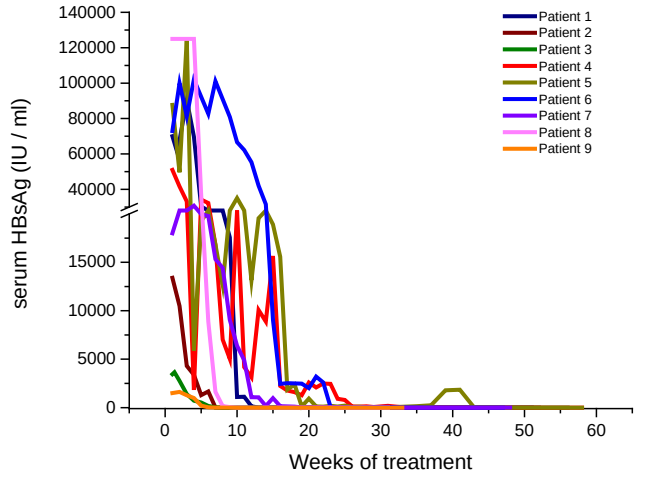
REP 102 trial
REP 2139-Ca + partial immunotherapy

REP 201 trial
REP 2139-Ca + Pegasys® + ETV

NAP-induced clearance of serum HBsAg (on treatment dynamics)

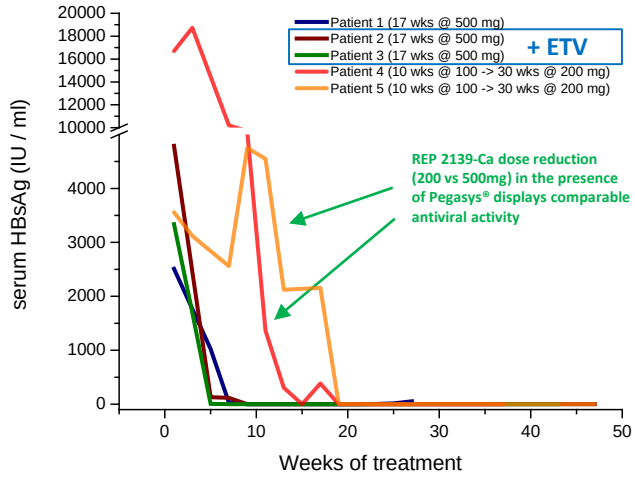


Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	934	0.14	3.82
2	1885	0.38	3.70
2 (2)	294	0.30	2.99
3	384	0.01	4.58
4	74330	0.03	6.39
5	158180	0.01	7.20
6	36996	7.00	3.72
7	4673	43.70	2.03



Immunotherapy present during last 13-26 weeks of treatment

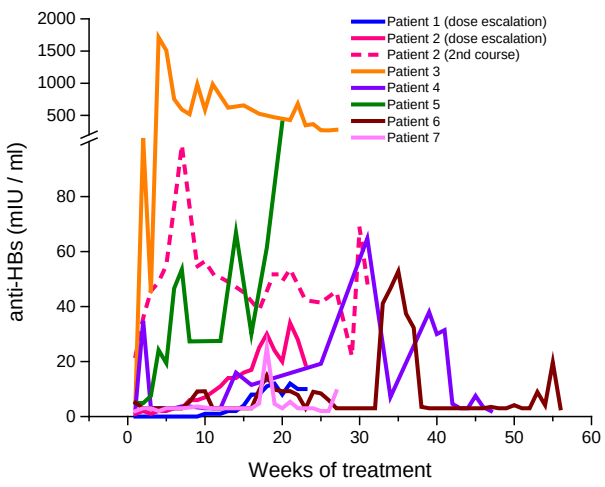
Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	70050	0.03	6.37
2	13400	0.01	6.13
3	3450	0.03	5.06
4	50994	0.03	6.23
5	87690	0.01	6.94
6	72968	0.02	6.56
7	17988	0.03	5.78
8	125000	0.02	6.80
9	1504	0.02	4.88

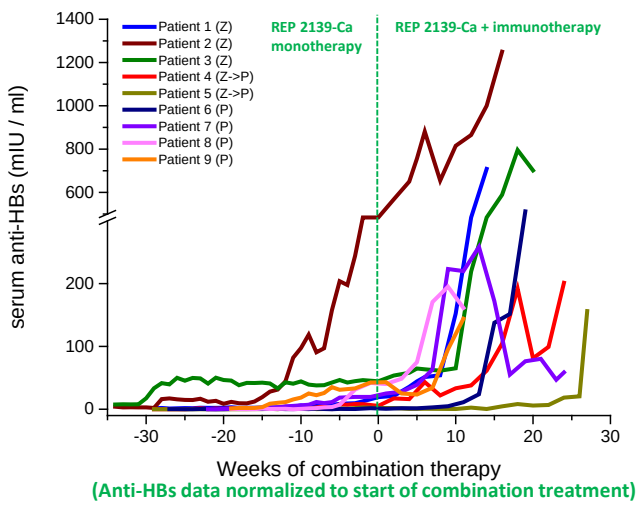


Pegasys® present throughout treatment

Patient	Serum HBsAg (IU / ml)		Log reduction
	Start	Lowest observed	
1	2510	0.08	4.50
2	4789	0.03	5.20
3	3338	0.01	5.52
4	16705	0.02	5.92
5	3558	0.01	5.55

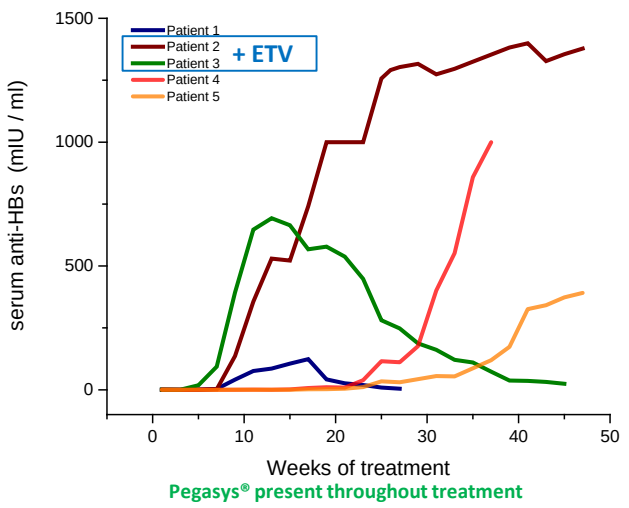
HBsAg clearance permits restoration of functional anti-HBs response (on treatment dynamics)





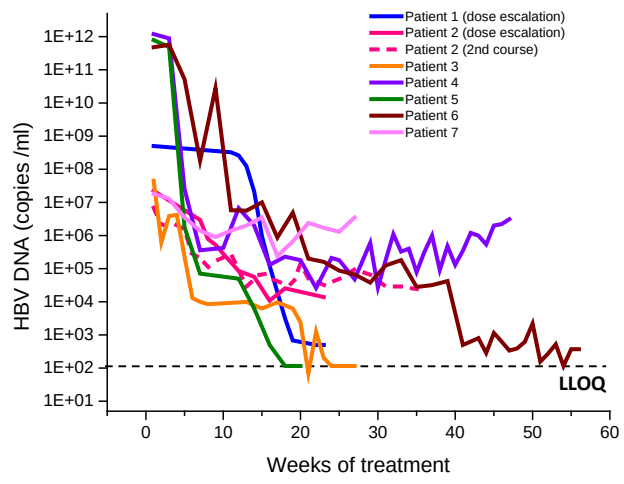
(Anti-HBs data normalized to start of combination treatment)

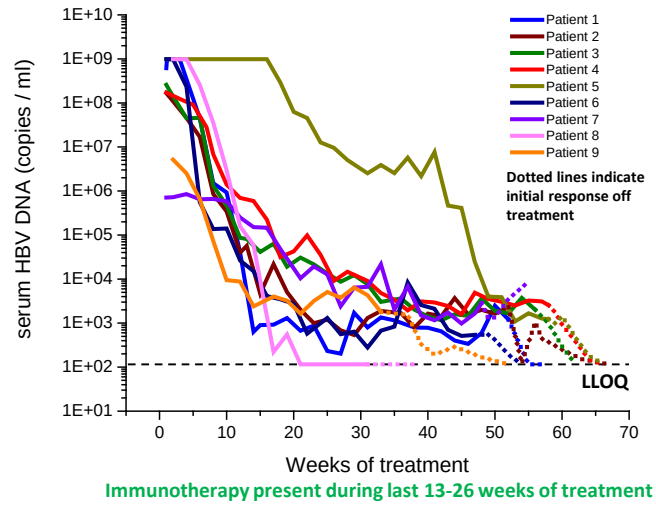
Z = Zadaxin® (13 weeks), P = Pegasys®(13 weeks)



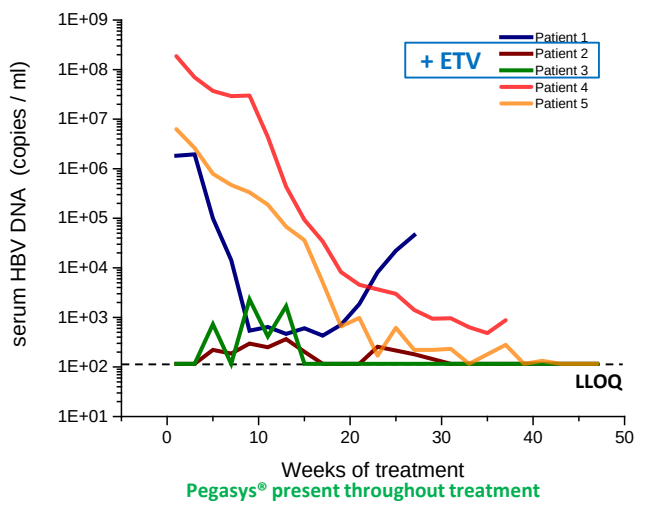
Pegasys® present throughout treatment

NAP-induced clearance of serum HBV DNA





Immunotherapy present during last 13-26 weeks of treatment



Pegasys® present throughout treatment

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SVR data and conclusions

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Sustained Virologic Response (SVR) Off Treatment

All protocols

Trial	REP 101 protocol	REP 102 protocol	REP 201 protocol
Treatment	REP 2055	REP 2139-Ca + 13-26 weeks Pegasys® and / or Zadaxin®	REP 2139-Ca + 48 weeks Pegasys™ (+ ETV in 2 patients)
Patients enrolled	8	12	5
Patients with HBsAg reduction or clearance	7	10	5
Patients receiving immunotherapy	0	9	5
Patients with short term (~3 M) SVR* off treatment	3	8	4
Patients with long term SVR* (> 12 months)	**2**	**4**	**4**

* serum HBV DNA < 500 CPM

CONCLUSIONS

- NAP therapy in combination with immunotherapy and ETV appears safe
- Combining REP 2139-Ca and immunotherapy has a synergistic antiviral effect (immunostimulation in the absence of HBsAg).
- NAP-based combination therapy may substantially increase the SVR rate compared to existing treatments for chronic hepatitis B infection

On treatment data

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