Case Report

The Ambush: A team approach

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Case Presentation

Mr. X, 83 years old male, known to have Carcinoma Prostate on Immunotherapy (Calutide & Lupride) for 4 months, came with pruritis and loss of appetite of 1-week, and yellowish discolouration of skin and conjunctiva for 2 days. There was no previous history of jaundice or blood transfusion.

On the basic evaluation of jaundice, he was diagnosed to have HBsAg positive status with a bilirubin of 4 mg/dl. Further evaluation for Hepatitis B infection revealed IgM anti-HBC-Reactive, HBeAg-Positive and HBV-DNA viral load of 4,38,50000 IU/ML.

He was started on Tenofovir Alafenamide (TAF) 25 mg/day and advised follow-up.

Within 5 days, he presented to ER with breathing difficulty associated with abdominal distension- new onset ascites- and admitted for further management.

USG Abdomen revealed normal liver with massive ascites which was evaluated further by examining ascitic fluid.

He had hyponatremia – possibly dilutional. Total bilirubin increased to 20 mg/dl. He was diagnosed as acute on chronic hepatitis, with decompensation. HBV infection was in replicative phase, as HBeAg was positive. He had no risk factor for acquiring acute hepatitis B infection.

Ascitic fluid analysis revealed high Serum-Ascites Albumin Gradient (SAAG) with low protein ascites – suggestive of portal hypertension and no spontaneous bacterial peritonitis.

Patient developed progressive jaundice with mild elevation of serum creatinine for which nephrologist opinion was obtained – suggested possiblity of Fanconi's syndrome and tenofovir was replaced by entecavir 1mg per day.

HBeAg and IgM-Anti HBc was rechecked after 10 days found to be persistently reactive and decided on combined antivirals

started (Tenofovir Alafenamide 25 mg/day + Entecavir 1 mg/day).

Patient's total bilirubin was persistently above 30 mg/dl and advised for plasmapheresis when it went above 40 mg/dl. He underwent 7 cycles of plasmapheresis within 2-weeks and his bilirubin stabilized to be within 20 mg/dl. He was discharged with dual antivirals, diuretics and anti-encephalopathy measures once bilirubin was stable, < 20 mg/dl. After 10 days, his bilirubin levels were showing a declining trend (As OPD basis) and further plasmapheresis was withheld. He was kept on combined anti-viral therapy.

Investigations	**Day-0**	**Day-5**	**Day-11**	**Day-14**	**Day-16**	**Day-17**	**Day-19**	**Day-25**	**Day-26**	**Day-28**	**Day-32**	**Day-43**	**Day-78**
BIL(Total)	12.5	34	34.4	44.	23.96	31.7	24.54	38.3	39.8	30.7	20.1	12.7	1.2
BIL(Direct)	4.8	23.9	20.	28.2	136.4	19.3	14.58	23.6	27.1	22.3	15.2	9.4	1.0
AST	462	783.1	374.9	276.4	127.3	173.4	190.7	195.7	198.2	159.1	160	182	34
ALT	486	831.6	478.8	358.7		152.1	121.4	162	160.5	110.1	105	170	29
SAP	137		50.4	62.2									76
UREA		47.2	50		69.7		57.2	50.8		54.6	50	59	21
CREAT		1.58	1.64		1.41		1.34	1.46		1.74	1.6	1.2	0.9
IgM Anti-HBc	Reactive				Reactive								
HBeAg	Positive				Reactive								Negative
HBV-DNA	4.385 crores												Not detected
PLEX				1	2	3	4	5	6	7			
	TAF	ETV					TAF+ETV						TAF

He was monitored on a weekly basis and had gradual improvement in his urine output. No abdominal distension or pedal edema.

After 2 weeks his blood investigations revealed normal creatinine levels and total bilirubin of 12mg/dl and his diuretics were reduced. After a month, his bilirubin was 3.1mg/dl and he had no specific complaints – advised to stop diuretics and to continue dual antivirals only.

After 2 months his HBeAg was negative and HBV-DNA viral load was not detected (CVR-Complete virological suppression). His bilirubin levels and creatinine levels were within normal limits. He was put on tenofovir alafenamide 25mg per day alone. He was planned for orchidectomy and prostatectomy for Carcinoma of Prostate.

This case suggested a re-activation of an occult hepatitis-B infection. This mandated a proper search for hidden Hepatitis-B virus beyond our routine viral screening tests done before any immunosuppressive therapy or immunotherapy. Reactivation of an occult-HBV infection can cause acute-on-chronic liver failure (ACLF) necessitating even liver transplantation.

In this case it was a team approach, with Nephrologist, for plamapheresis with proper counselling of the outcomes & after setting realistic goals to the patients and their wards with regard to plasmapheresis as a bridge to liver transplantation.

Discussion

This is the first case to be reported on the utility of combination therapy of ETV+TDF, with plasmapheresis, in ACLF due to reactivation of an occult HBV infection when started on immunotherapy, who was otherwise a candidate for an urgent liver transplantation.

Combination therapy with a nucleoside and a nucleotide is recommended by the current European Association for the Study of the Liver clinical practice guideline based on *in vitro* cross-resistance data and insufficient clinical data [1]. European study showed that combination therapy with ETV plus TDF is efficient and safe in patients with viral resistance patterns or with only partial antiviral responses to prior antiviral therapies.

The antiviral efficacy of ETV-TDF combination therapy in patients infected with MDR HBV strains as rescue therapy [2]. ETV-TDF combination therapy was well tolerated without serious adverse events, including renal dysfunction. ETV-TDF treatment is effective in patients with MDR and produces a relatively high rate of complete virologic suppression at an early time point, even in patients with triple resistance to LAM, ETV, and ADV. Liver cirrhosis was not associated with complete virologic suppression, which indicated that the antiviral efficacy of treatment with ETV-TDF combination is not affected by the presence of advanced liver disease.

A prior study that evaluated the efficacy of ETV-TDF combination therapy in CHB patients pretreated with antiviral drugs showed that 51 of 57 patients (89.5%) achieved undetectable HBV DNA during the rescue therapy [3].

An appropriate combination of the most potent drugs with high genetic barriers and compensatory cross-resistance profiles, such as ETV and TDF, is necessary for these difficult-to-treat patients. Therefore, ETV-TDF combination therapy should be considered the treatment of choice in such

patients to achieve early and sustained viral suppression.

Treating patients infected with HBV strains resistant to ETV with combination therapy with ETV plus TDF can have an additional benefit over TDF monotherapy, especially with regard to a reduced risk of developing subsequent resistance.

Conclusion

This case emphasises the importance of screening for an occult HBV infection, in addition to the routine viral screening done before any immunosuppressive therapy or immunotherapy. This case also portrays the efficacy, safety & utility of combined anti-viral therapy of Tenofovir Alafenamide with Entecavir in HBV reactivation leading to ACLF. This case also shows the utility of plasmapheresis in ACLF not only as a bridge to transplantation but also as a component of treatment in ACLF with combined-antiviral therapy.

References

[1] European Association for the Study of the Liver. 2012. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J. Hepatol. 57:167–185.

[2] Efficacy of Entecavir-Tenofovir combination therapy for chronic hepatitis b patients with multidrug-resistant strains. Antimicrob Agents Chemother. 2014;58(11):6710–6716.

[3] Petersen J, et al. 2012. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. J. Hepatol. 56:520–526.