LAMIVUDINE-RESISTANT MUTATION DETECTED AMONG TREATMENT-NAÏVE HEPATITIS B PATIENTS IS COMMON AND MAY BE ASSOCIATED WITH TREATMENT FAILURE

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1. Background

- Pre-existing antiviral resistance (AVR) mutation among treatment-naive hepatitis B patients is believed to occur at avery low frequency.
- Pre-existing lamivudine-resistant mutation using direct sequencing was reported among 10% of patients.[1,2]
- Pre-existing lamivudine mutation was reported in 1-2% nucleoside-naive entecavir patients.[3]
- Various laboratory methods have variable sensitivity to detect AVR.
  - *Line probe assays more sensitive than direct sequencing*
- The clinical significance of pre-existing antiviral resistance mutations is unknown.
  - *Exact prevalence in clinical practice*
  - *Optimal methods of detection*
  - *Influence on initial treatment regimens*
  - *Response to first line antiviral therapy*

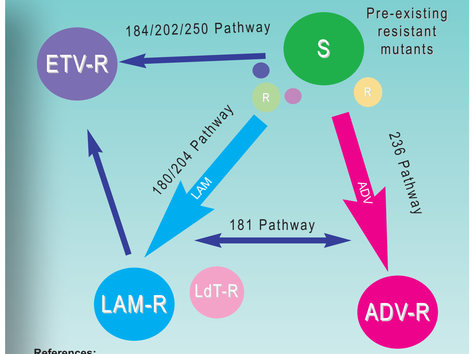
2. Aims

1. To document the prevalence of antiviral resistance (AVR) mutations among untreated HBV patients using a line probe assay.
2. To determine whether AVR mutations are associated with reduced efficacy to antiviral therapy.

3. Patients and Methods

- Consecutive untreated adult patients with chronic hepatitis B attending the liver clinics of University Health Network and Mount Sinai Hospital (Toronto, Canada) from 1/2007 – 03/2008 were tested for AVR.
- Demographic data were recorded.
- Patients were deemed to be *treatment-naïve* after a careful treatment history on 2 separate occasions, corroborated by a family member, where possible.
- Routine bloodwork (liver panel, CBC, PT/INR and HBV serology) and abdominal ultrasound were performed at enrollment.
- HBV DNA was quantified by PCR asssay (Roche Ampliprep, LLQ 6 IU/ml).
- HBV genotype and AVR mutations were detected using INNO-LiPA HBV DRv3 (InnoGenetics, Gent, Belgium).
- Statistical analysis was performed using SPSS v13 (SPSS, Chicago, IL).

HBV Resistance Pathways



References:

1. Kobayashi S, Ide T, Sata M. 2001. Detection of YMDD motif mutations in some lamivudine untreated asymptomatic hepatitis B virus carriers. *J. Hepatol.* 34(4): 584 – 586.
2. Matsuda F, Suzuki Y, Suzuki A , et. al. 2004. Low rate of YMDD motif mutations in polymerase gene of hepatitis B virus in chronically infected patients not treated with lamivudine. *J. Gastroenterol.* 39(1) 34 – 40.
3. Colonno RJ, Rose R, Baldick CJ, et. al. 2006. Entecavir resistance is rare in nucleoside naïve patients with hepatitis B. *Hepatology* 44 (6) 1656 – 1665.

4. Results

- Mutations associated with rt180/204 resistance pathway in up to 12% treatment-naïve patients
  - *mutant virus was always detected as a mixed species along with wild type virus*
  - *rtL180M+rtM204V occurred together in >90%*
  - *isolated cases of rtL80V/I or rtL180M*
- Entecavir-resistant mutation was detected in 5% treatment-naïve patients
- Mutations associated with rt181/236 resistance pathway occurred in 0-1% patients

Clinical Course of Patients with AVR

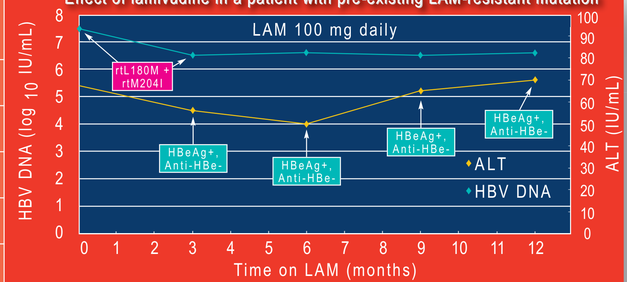
- Of the patients with pre-existing rt180/204 mutation
  - *12 immune tolerant phase*
  - *10 inactive carrier state*
- 9 patients met criteria for antiviral therapy
  - *2 received tenofovir monotherapy*
  - *1 received lamivudine monotherapy*
  - *1 received adefovir monotherapy*
  - *1 received pegylated interferon*
  - *4 still contemplating therapy*

Patient Characteristics (N = 313)	
Mean Age (years)	48 ± 13
%Male : %Female	61:39
% HBeAg-positive	41
Mean ALT (U/L)	84 ± 171
Mean HBV DNA (IU/mL)	7.0 ± 2.4
Mean Platelets (Bil/L)	228 ± 67
% Cirrhosis (on ultrasound or liver biopsy)	12
HBV genotype (A/B/C/D)	6/35/55/3

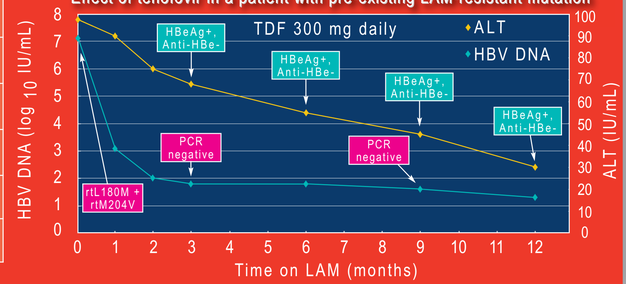
	OR (95% CI)	P-value
Male gender	28 (1.8 - 650)	0.04
HBV DNA < 6 log $_{10}$ IU/mL	0.2 (0.07 -0.8)	0.02
HBeAg-positivity	6.0 (0.3 - 111)	0.24
ALT > 2 x ULN	1.1 (0.9 - 1.3)	0.94

RT Substitution	Frequency (%)
L80V/I	4
V173L	0
L180M	3
M204V/I	12
A181V/T	1
I233V	1
N236T	0
A194T	0.7
T184G/L	1
S202C/I	2
M250V	2

Effect of lamivudine in a patient with pre-existing LAM-resistant mutation



Effect of tenofovir in a patient with pre-existing LAM-resistant mutation



5. Summary

- Mutations associated with rt180/204 resistance pathway were common among treatment-naïve patients (12%).
- Those associated with the rt181/236 nucleotide pathway were much less common (1%).
- Among patients with pre-existing rt180/204 mutation
  - *LAM monotherapy led to treatment failure*
  - *ADV or TDF monotherapy showed no reduction in efficacy*

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6. Conclusions

- Antiviral resistance mutations can be found among treatment-naïve patients
  - *rt180/204 mutations relatively common*
  - *rt184/202/250 mutations also detectable*
  - *rt181/236 mutation much less common*
- Pre-existing mutation leads to antiviral treatment failure
  - *Mechanism of early or late treatment failure*
- Lamivudine monotherapy should be abandoned as a first line therapy for chronic hepatitis B.
- AVR testing among treatment-naïve patients is important, in order to tailor antiviral therapy and to optimize treatment.
- However, further studies are required to determine the role of AVR testing in routine clinical practice.

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