

# Journal Club

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# 96 weeks combination of adefovir dipivoxil plus emtricitabine vs. adefovir dipivoxil monotherapy in the treatment of chronic hepatitis B

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# Background

- Hepatitis B Infection is chronically infected in about 350 million people worldwide.
- In order to delay & prevent the occurrence of drug resistant mutants associated with the treatment of chronic hepatitis B Infection, long term combination therapy is being developed.

# Background

- The study tried to determine the efficacy of adefovir dipivoxil (ADV) plus emtricitabine (FTC) combination therapy in chronic HBV infection.
- HBV replication is catalyzed by the viral polymerase reverse transcription step.

# Background

- Development of antiretroviral nucleoside and nucleotide analogues
- HBeAg seroconversion with 48 weeks of currently approved analogues only results in around 20% HBeAg Seroconversion.
- Those that have developed seroconversion, disease remission is sustained in 50-70% of cases.

# Background

- Successful treatment for HBeAg – positive patients with active viral replication
  - HBeAg seroconversion (loss of HbeAg with development of anti-HBe for 2 consecutive readings > 12 weeks apart)
    - Early: within 96 weeks of treatment
    - Late: occurring beyond 96 weeks of treatment
  - Normalization of alanine aminotransferase (ALT)
  - Suppression of Serum HBV DNA <100,000 copies/ml
- Aim of the study was to determine whether prolonged ADV plus FTC combination therapy is well tolerated and efficacious for chronic HBV.

# Methods

- 30 HBeAg – positive, treatment naïve, chronic HBV patients
- Recruited Queen Mary Hospital, Hong Kong SAR
- Double blind study, randomly assigned

# Methods

- Group 1: oral adefovir dipivoxil 10mg QD + Placebo
- Group 2: oral adefovir dipivoxil 10mg QD + emtricitabine 200mg QD
- Duration of therapy for 48 weeks, entered a follow – on study for additional 48 weeks
- HbeAg seroconversion at week 96, therapy was stopped
- HBeAg + at week 96, were all switched to ADV monotherapy and continued until 6 months after HBeAg seroconversion.



# Methods

## ■ End of Treatment

- Normalization of serum ALT levels and suppression of serum HBV DNA below the lower limit of detection by PCR assay.
- Post – Treatment Relapse:
  - ALT > 2 times upper limit +
  - HBV DNA by >1 log<sub>10</sub> copies/ml
    - HBV DNA > 10,000 at the end of treatment
    - HBV DNA > 10,000 in those with end of treatment HBV DNA < 10,000

# Methods

- Resistance surveillance was performed on a subset of patients with detectable viremia at week 96
- Percutaneous Liver Biopsy was done at baseline

# Results

- Statistical analysis: Mann-Whitney U test, Fisher's exact test, chi-square test
- Baseline demographic for patients in the combination and monotherapy groups
  - Table 1

# HBV DNA Suppression

- Combination group at week 96 higher decrease in HBV DNA when compared to monotherapy group
  - Figure 1.
- 78.5 % (11 of 14) in combination group had HBV DNA < 300 copies/cc when compared 37.5% ADV monotherapy group (6 of 16).
  - Figure 2 and Table 3.

## Normalization of Serum ALT and Serum HBV DNA below lower limit of detection

- 78.6 % (11 of 14) in combination group had normal ALT at 96 weeks and 62.5% in the monotherapy group.
- Combination group had Normal ALT and HBV DNA level less than the lower limit of detection at week 96 when compared to the monotherapy group (78.6% vs 37.5%)

# Drug Resistance

- 4 of 30 patients had virological breakthrough with  $> 1$  log increase in serum HBV DNA
  - 21.4% in combination group
  - 6.3% in monotherapy group
- Breakthrough occurred at 64, 72, & 72 and 96 week.

# HBeAg Seroconversion

- Early conversion in combination group occurred in 14.3% patients and 25.0% in monotherapy group at 96 weeks.
  - 6 patients responded at 96 weeks, combination treatment was discontinued.
- Late Seroconversion
  - 24 patients rolled over to monotherapy (beyond week 96)
  - 4 patient responded on monotherapy (therapy was discontinued after 6 month consolidation period)
  - Table 3

# Post-Treatment Relapse

- 10 patients with seroconversion followed up for median of 10.6 months after discontinuation of therapy.
  - 50% (5 of 10) developed post-treatment relapse
    - 33.3% (2 of 6) in early seroconverters
    - 75.0% (3 of 4) in late seroconverters



# Discussion / Limitations

- Disease remission – Follow up.
- Small sample size
  - Rate of HbeAg seroconversion is similar between the 2 groups, due to small sample size?
- Only 2 study groups:
  - Group 1: oral adefovir dipivoxil 10mg QD + Placebo : Control Group?
  - Group 2: oral adefovir dipivoxil 10mg QD + emtricitabine 200mg QD
  - Group 3: Oral Emtricitabine ??
- Virologic breakthrough with 4 of 30 patients.
  - 21.4% in combination group
  - 6.3% in monotherapy group
- 50% (5 of 10) developed post-treatment relapse
- Failed to demonstrate that the use of combination therapy could reduce the emergence of ADV drug resistance since the study was not powered for this endpoint.

Randomized, double-blind study comparing adefovir dipivoxil (ADV) plus emtricitabine (FTC) combination therapy versus adv alone in HBeAg (+) chronic hepatitis B: efficacy and mechanisms of treatment response *Hepatology*. 40(4 Supl 1):272A, 2004.

- **Background:** Improvement of treatment response in chronic hepatitis B requires new antiviral regimens and better understanding of viral and host factors associated with sustained control of HBV replication.
- **Aims:** i) To compare the efficacy of a new combination therapy of ADV plus FTC versus ADV alone; ii) To examine early HBV kinetics and virus-specific T-cell reactivity to gain understanding of the mechanisms of successful HBV control.

- **Methods:** Thirty treatment naive, HBeAg (+) patients (HBV genotype B, n=9; genotype C, n=21) with ALT > 1.3xULN were randomized to receive ADV 10 mg + FTC 200 mg qd (Group A, n=14) or ADV 10 mg + placebo qd (Group B, n=16) for 48 weeks.
- **Results:** The combination (ADV+FTC) therapy showed greater antiviral activity compared to ADV alone: median log<sub>10</sub> reduction of viremia at treatment week 24 was 3.14 vs 2.16 (p=0.004); at TW48 - 3.48 vs. 2.22 (p=0.036), respectively. HBeAg seroconversion occurred in 3 patients - Group A (n=2) and Group B (n=1). Patients on combination treatment were more likely to be fast responders than those on monotherapy (p=0.01).
- **Conclusions:** i) ADV plus FTC combination therapy shows faster and greater HBV suppression in comparison with ADV alone; ii) this faster suppression is reflected in the second phase viral kinetic parameters; and iii) early HBV suppression during therapy is associated with enhanced antiviral immunity.

Sequential combination therapy leads to biochemical and histological improvement despite low ongoing intrahepatic hepatitis B virus replication. [Journal Article. Research Support, Non-U.S. Gov't] Antiviral Therapy. 13(1):57-66, 2008.

- **BACKGROUND:** We previously reported that 48 weeks of combination therapy with pegylated interferon-alpha2b (PEG-IFN-alpha2b) and adefovir dipivoxil (ADV) in patients with chronic hepatitis B led to marked decreases of hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) (-2.4 log<sub>10</sub> copies/ml). Combination therapy was followed by 96 weeks of ADV monotherapy.
- **METHODS:** Report on the final outcome after 144 weeks of sequential antiviral treatment. 24 patients were analysed, triplet liver biopsies (taken at baseline, week 48 and week 144) were available from 16 patients.

- **RESULTS:** At week 144, 12/15 patients positive for hepatitis B virus e antigen (HBeAg) had lost HBeAg, alanine transaminase (ALT) levels were normal in 23 patients (96%), median serum HBV DNA had decreased by -4.9 log<sub>10</sub> copies/ml and was undetectable (<100 copies/ml) in 11/24 individuals (46%). Median total intrahepatic HBV DNA had decreased by -2.2 log. Although no further significant DNA changes occurred between week 48 and week 144, two years of ADV monotherapy proved capable of controlling DNA levels in most patients. Analysis of intrahepatic HBV DNA species demonstrated that combination therapy with PEG-IFN-alpha2b and ADV inhibited viral productivity by 99% and subsequent ADV monotherapy by 76%, respectively. Virus suppression to undetectability within the first 12 weeks of treatment was strongly associated with long-term virological response and HBeAg and hepatitis B virus surface antigen HBsAg seroconversion. Histological improvement was determined in 11/16 patients at week 144. Two patients developed ADV resistance during the third year of treatment.
- **CONCLUSIONS:** Reduction of intrahepatic viral load achieved after 48 weeks of combination therapy with PEG-IFN-alpha2b and ADV was maintained in the following 96 weeks of ADV monotherapy and translated into long-term clinical benefit for most of the treated patients.

Adefovir and lamivudine in combination compared with adefovir monotherapy in HBeAg-negative adults with chronic hepatitis B virus infection and clinical or virologic resistance to lamivudine: A retrospective, multicenter, nonrandomized, open-label study. [Journal Article] *Clinical Therapeutics*. 30(2):317-23, 2008 Feb.

- **Objectives:** The aim of this study was to assess the therapeutic effectiveness of adefovir dipivoxil (ADV), administered in combination with lamivudine (LAM) or as monotherapy, and the rate of resistance to ADV, in hepatitis B e antigen (HBeAg)-negative adult patients with chronic hepatitis B virus (HBV) infection and clinical or virologic resistance to LAM.
- **Methods:** Patients were selected if they received ADV 10 mg PO QD + LAM 100 mg QD PO or ADV 10 mg PO QD as monotherapy for 24 to 32 months. End points were the proportions of patients who achieved virologic response (undetectable HBV-DNA [ $<3.3 \log(10)$  copies/mL]) and biochemical response (normalization [ $<40$  IU/L] of alanine aminotransferase [ALT]), and the proportions in whom resistance to ADV (rebound serum HBV-DNA  $>1 \log(10)$  copies/mL compared with on-treatment nadir, as confirmed on molecular analysis) was found.

- Results: Data from 70 patients were included. The median duration of the pharmacologic treatment in the 2 groups of patients was 28 months (range, 24-32 months). By month 3, virologic response was achieved in 30 patients (83%) in the ADV + LAM group and in 26 patients (76%) in the ADV monotherapy group. At 12 months, virologic response was achieved in 5 additional patients in the ADV + LAM group and 2 additional patients in the ADV monotherapy group. Biochemical response was found to be time dependent: in the 2 groups, the rates of biochemical response were, respectively, 56% and 54% at month 3, 80% and 71% at month 6, and 96% and 79% at month 12, persisting up to the end of the study period. The rates of clinical resistance to ADV were 3% with ADV + LAM and 18% with ADV monotherapy (with a 6% rate of resistance due to mutation in the monotherapy group).
- Conclusion: ADV, administered in combination with LAM or as monotherapy, appeared to be effective in this small, selected group of HBeAg-negative patients with clinical or virologic resistance to LAM, especially in those with low pretreatment HBV-DNA levels, high ALT levels, and low fibrosis scores.