Treatment Options for Chronic Hepatitis B

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Treatment of Chronic Hepatitis B

- can be prevented by vaccination (part of infant series since 1992-3)
- goal of drug therapy is to suppress HBV viral load (HBV DNA PCR), ↓ hepatic inflammation and fibrosis
- cure, defined as Hepatitis B e antigen conversion to e antibody, is rarely possible in some patients:

  e Ag+/e AB- → e Ag-/e AB+
- ultimate goal is to prevent end-stage liver disease (ESLD), cirrhosis &/or hepatocellular carcinoma
- current standard of care is evolving from monotherapy to combination therapy
- flares can occur with cessation of treatment

NIH Consensus Development Conference Statement on the Management of Hepatitis B, October 2008.

Indications for Hepatitis B Treatment-1

Patients for whom treatment is indicated:

- liver failure
- cirrhosis complications
- receiving immunosuppressive therapy
- infants born to HBsAg+ mothers
- reactivation of chronic HBV

Patients for whom therapy *may* be indicated:

- in the immune active phase, defined by the presence of elevated HBV DNA levels, with or without HBeAg, and evidence of active inflammation (ALT level elevation or active inflammation on liver histology)

NIH Consensus Development Conference Statement on the Management of Hepatitis B, October 2008.

Indications for Hepatitis B Treatment-2

- some treatment algorithms base specific recommendations on a combination of factors such as HBV viral load, ALT level and liver histology[1]
- most published reports of hepatitis therapy use changes in short-term parameters to infer likelihood of long-term benefit...[2]
  - virologic
  - biochemical
  - histologic
- approved therapies are associated with improvements in intermediate biomarkers, including… [2]
  - decreases in HBV DNA
  - HBeAg loss/seroconversion
  - decreases in ALT levels
  - improvement in liver histology

1. Keefe EB et al. A treatment algorithm for the management of chronic hepatitis B infection in the U.S.: 2008 update. Clin Gastro and Hepat 2008:1315-41. 2. NIH Consensus Development Conference Statement on the Management of Hepatitis B, October 2008.

Interferon (IFN) alfa-2a & -2b

- endogenous immunomodulator, produced as recombinant products
- Method of Action (MOA): unknown-- may prevent virus penetration and/or promote synthesis of RNAases & reparative proteins
- PK: pegylated forms achieve higher, more durable levels, permitting less frequent administration (once weekly)
- route: SC for peg-IFN, given as a defined course of 16-48 weeks

Interferon (IFN) alfa-2a & -2b

- adverse effects: flu-like symptoms, depression/ suicide, neutropenia & other hematologic abnormalities, thyroid dysfunction, headache, nausea, hair loss
- contraindications:
  - autoimmune disorders
  - caution in patients with h/o depression
- resistance: not yet described
- time to HBV DNA decline longer than that seen with nucleos(t)ides

Pros/cons of chronic HBV treatment with nucleos(t)ides

- once daily oral administration
- associated with faster viral load suppression than IFN
- useful in treating prior IFN non-responders
- if d/c'd prematurely, associated with resurgence of HBV DNA or reactivation (flare)
- long-term use (as monotherapy) can be compromised by development of resistance except for entecavir & tenofovir (no resistance seen after 5 yrs of therapy)
- some are associated with renal toxicity, myopathy (muscle weakness or pain), mitochondrial toxicity

Lamivudine (3TC), Emtricitabine (FTC)

- synthetic cytosine analogs
- in vitro activity: HBV, HIV-1
- 3TC was 1st nucleoside analog approved for treatment of chronic HBV
- MOA: triphosphorylated to its active form; inhibits HBV DNA polymerase and causes DNA chain termination
- PK: 3TC intracellular half-life longer in HBV-infected cells (17-19 hrs) than in HIV-infected (10.5-15.5 hrs); FTC half-life longer in both
- permits once daily 3TC administration at lower dose, 100 mg, compared to 300 mg for HIV; FTC dose 200 mg qd

Lamivudine (3TC), Emtricitabine (FTC)

- similar efficacy to interferon alfa
- HBeAg seroconversion occurs in ~17% and is durable x 3 yrs in 70%
- adverse effects: very well-tolerated, occasional headache
- resistance: incidence increases with duration of use and is common by the end of 1 yr of monotherapy
  - YMDD and pre-core mutants possible
  - 3TC-resistance results in cross-resistance to nucleo**s**ides (entecavir) but not to nucleo**t**ides (tenofovir, adefovir)

Entecavir

- guanosine analog
- MOA: triphosphorylation required-- inhibits viral DNA polymerase and terminates viral DNA prolongation
- in vitro activity: HBV, significantly lesser activity against HIV-1 and not indicated for treatment of HIV
- PK: oral bioavailability ~100% but is decreased by food so must be administered on empty stomach; intracellular half-life 15 hrs permits once daily dosing
- route: oral, dosed on empty stomach

Entecavir

- dose varies according to prior treatment status:
  - 0.5 mg once daily for naïve patients
  - 1 mg once daily for those previously treated
- renal excretion
- adverse reactions: generally well-tolerated--headache, fatigue, dizziness, nausea
- resistance: not yet defined
- should not be used for HBV in HIV co-infected persons who are not yet ready for HIV therapy in order to avoid HIV resistance development

Tenofovir (TDF), Adefovir (ADF)

- MOA: nucleotide analogs that inhibit viral DNA polymerase and terminate viral DNA elongation; require diphosphorylation by cellular kinases
- in vitro activity: HBV, HIV-1 (adefovir not active at 10 mg HBV dose)
- PK: both have long half-lives that permit once daily dosing
- renal excretion
- route: oral (ADF 10 mg/d, TDF 300 mg/d)
- adverse reactions: nephrotoxicity (adefovir has narrower therapeutic index than tenofovir), mitochondrial toxicity, myopathy, bone toxicity

Tenofovir (TDF), Adefovir (ADF)

- resistance: uncommon
- TDF more effective than ADF in a randomized, controlled trial*
- TDF is the drug of choice for HIV-coinfected patients when both diseases will be treated, and should be paired with 3TC (lamivudine) or FTC (emtricitabine) to provide combo therapy for both chronic HBV & HIV

*Marcellin P et al. NEJM 12/4/08