Liver Disease Research

Updates

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Liver Disease Research

- What is research?
- Types of Research
- Research in various types of liver diseases
- Funding for research
- Future Research in liver diseases diagnosis and treatment

What is Research?

- Main Entry: research
  - Pronunciation: riˈsər ch, riˈrē-
- Function: noun
  - Etymology: Middle French, from French, from Old French, from re- + cercher, sercher to search -- more at SEARCH
  - 1: careful or diligent search
  - 2: studious inquiry or examination; especially: investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws
  - 3: the collecting of information about a particular subject

Types of Research

- Basic Research
- Clinical Research
- Translational Research
Basic Research

- Research using cells like liver cells (hepatocytes)
- Research using animals (mice, chimpanzees etc.)

Clinical Research

- Retrospective collection and analysis of data to evaluate epidemiology, prevalence, natural history and outcome of treatments
- Prospective study of above information about various liver diseases
- Drug trials for efficacy of new and approved drugs

Research: Liver diseases

- Viral Hepatitis B, C and other viruses
- Alcohol related liver disease
- Non-alcoholic fatty liver disease
- Autoimmune Liver diseases
- Complications of Cirrhosis
- Liver Cancer
- Liver Transplantation

Research: Hepatitis B

- Vaccine
- Treatment of Hepatitis B: new drugs
- Hepatitis B and liver cancer
- Hepatitis B and liver transplantation
Hepatitis B

• Vaccine available and protects for many yrs.
• Combination Hepatitis A and B vaccine available
• All patients with liver disease should get vaccine against Hepatitis A and B

HEPATITIS A VACCINES

• Highly immunogenic
  • 97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose
• Highly efficacious
  • In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose

HEPATITIS A VACCINES

**Recommended Dosages of Hepatitis A Vaccines**

<table>
<thead>
<tr>
<th>Schedule Vaccine</th>
<th>Age (yrs)</th>
<th>Dose (mL)</th>
<th>Volume (2-Dose) (mos)</th>
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<tr>
<td>HAVRIX **</td>
<td>2-18</td>
<td>720 (EL.U.*)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>1,440</td>
<td>1.0</td>
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<tr>
<td>VAQTA **</td>
<td>2-18</td>
<td>25 (U**)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>50</td>
<td>1.0</td>
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</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units
** Units
# has 2-phenoxyethanol as a preservative
## has no preservative

**Commercially Available Recombinant Vaccines**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Source</th>
<th>Manufacturer</th>
<th>Licensed in U.S.</th>
</tr>
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<tbody>
<tr>
<td>Engerix-B</td>
<td>Yeast</td>
<td>SmithKline Beecham</td>
<td>Yes</td>
</tr>
<tr>
<td>Recombivax HB</td>
<td>Yeast</td>
<td>Merck</td>
<td>Yes</td>
</tr>
<tr>
<td>Binenugen</td>
<td>Yeast</td>
<td>Kaketsuken</td>
<td>No</td>
</tr>
<tr>
<td>Elicli-Bi-Wal</td>
<td>Yeast</td>
<td>Green Cross</td>
<td>No</td>
</tr>
<tr>
<td>Hepacomb</td>
<td>Yeast</td>
<td>Berna</td>
<td>No</td>
</tr>
<tr>
<td>Genhevac B</td>
<td>CHO cells</td>
<td>Pasteur-Merieux</td>
<td>No</td>
</tr>
<tr>
<td>r-HB Vaccine</td>
<td>CHO cells</td>
<td>Mitsubishi</td>
<td>No</td>
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*Chinese hamster ovary
Combination Vaccines

- Combination of Hepatitis A and B vaccines
- Twinrix: 18 yrs and older, combination of Havrix(720) and Engerix(20)
- Comvax: 6 weeks to 4 yrs, combination of Recombivax (%) and Pedvaxhib
- Pediarix: 6 weeks to 6 yrs, Engerix (10), infanrix (DTaP) and IPV
- All require 3 doses

Treatment of Hepatitis B

- Current Approved Drugs
  - Interferon, Lamivudine
  - Adefovir, Entecavir
- Drugs in Clinical Trials
  - Tenofivir, Telbuvidine
- Combination drugs in future

Research: Hepatitis C

- Treatment of Chronic Hepatitis
  - Current Treatment
  - New Drugs
- Basic research in Virology
  - Viral Kinetics
  - Viral resistance
- Vaccine for prevention and treatment

Nonresponder Growth Exceeds Treated Naïves

- Data on file.
- Growing nonresponder patient population
- naïve HCV patient population
- Nonresponding HCV patient population
Research: ASH and NAFLD

- Why only some people develop?
- Associated factors for both conditions
- Diagnosis of both conditions
- Natural history
- Pathogenesis
- Treatment of ASH and NASH

Clinical Trials: HCV Therapies in the Pipeline

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Phase</th>
<th>Description</th>
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<td>Viramidine</td>
<td>Ph. I</td>
<td>HCV polymerase inhibitor</td>
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<tr>
<td>Valeant</td>
<td>Multiferon</td>
<td>Ph. I</td>
<td>Therapeutic vaccine</td>
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<tr>
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<td>Interferon alfacon-1b+</td>
<td>Ph. II</td>
<td>Fusion albumin + IFN alpha</td>
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<td>Albuferon</td>
<td>Ph. II</td>
<td>Multispecific human alpha IFN</td>
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<td>Zadaxin</td>
<td>Ph. II</td>
<td>Thymosin alpha 1 immune modulator</td>
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<td>IC41</td>
<td>Ph. II</td>
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<tr>
<td>Chiron/CSL</td>
<td>MF59 vaccine</td>
<td>Ph. III</td>
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<td>Rebif</td>
<td>Ph. III</td>
<td>IFN beta</td>
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Wait for New Agents to Be Developed: New Therapies Will Not Be on the Market for the Next Several Years
Treatment of NAFLD

- No approved treatment
- Treatments in trial: Vitamin E, other alternative medicines
- Drugs in trials: urso-deoxy cholic acid, rosiglitazone, Pentoxifylline

Research: AIH and Overlap Syndromes

- Causes of autoimmune liver diseases
- Diagnosis of autoimmune hepatitis and overlap syndromes
- Treatment for both diseases

AIH: Treatment

- Relapse after drug withdrawal
- Drug toxicity
- Treatment failure despite compliance (9%)
- Incomplete response (13%)

AIH: Evolving Therapies
Normal Biliary tract

Primary Biliary Cirrhosis
- Chronic Cholestatic Liver Disease
- Female to male ratio 9:1
- Etiology unknown
- ? Autoimmune
- Genetic factors, HLA relationship
- Epidemiology: variability due to case finding

Diagnosis Of PBC
- Lab. Tests: elevated Alk. Phosh. >3-5 times normal
- Anti-mitochondrial antibody
- Imaging Studies: normal cholangiogram
- Liver biopsy

Complications Of PBC
- Chronic Cholestasis: Jaundice, hyperpigmentation, pruritus, Steatorrhea, malabsorption of fat soluble vitamins, Osteoporosis, Osteomalacia, hypercholesterolemia.
- Biliary Cirrhosis: portal hypertension, variceal bleeding, ascites
Treatment OF PBC

- Symptomatic: Cholestyramine
  Fat soluble vitamins
- Specific Rx: none proven
  various immunosuppressive agents
  Ursodeoxycholic acid
- Liver Transplantation

Primary Sclerosing Cholangitis

Research: Complications of Cirrhosis

- Portal hypertension and varices
- Ascites and spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatic encephalopathy
- Drugs in patients with cirrhosis
- Reversal of cirrhosis

Portal Hypertension

- Esophageal varices
- Gastric varices
- Portal hypertensive gastropathy
- GI Bleeding, anemia
Esophageal Varices

Bleeding Esophageal Varices

Variceal banding

Portal Hypertension

- Banding of esophageal varices
- Sclerotherapy
- Oral drugs: propranolol, nadolol
- IV octreotide
- TIPS
- Surgery
Hepatic Encephalopathy

- Current treatments: Lactulose, antibiotics, nutritional supplements
- New Treatments: new antibiotic rifaximin
  - Sodium Benzoate,

Research; Liver Cancer

- Best way to screen patients at high risk
- Treatment of liver cancer and new modalities
- New drugs for treatment and prevention of liver cancer
- Role of liver transplantation
- Why some patients develop liver cancer/

Funding for Liver Disease Research

- Various organizations
  - NIH, NIDDK, ALF
  - Academic centers
  - Other not for profit organizations
- Drug company sponsored research
  - New Drugs studies
  - Approved drugs for new use
  - Post-marketing study
Internet Sites For Information

- Liverfoundation.org
- Nih.gov, niddk.nih.gov
- ClinicalTrials.gov
- VA sponsored research
- Academic Center websites
- Illinois-liver.org

Thank you for your attention