Programs for Chronic HBV and HCV in Alaska Natives

Brian J McMahon MD, Liver Disease and Hepatitis Program Alaska Native Medical Center and Arctic Investigations Program, CDC
Misconceptions about Alaska

• Alaska is not part of Canada
• You can see Russia from Alaska (but not from Sarah Palin’s house)
• Contrary to Fox News, the Arctic ice is thinning
• Contrary to TV weatherman's maps, Alaska is not an island off California
How Young Children in UNITED STATES draw US MAP
ALL GOOD ALASKANS GRIND THEIR TEETH WHEN THEY COME ACROSS ONE OF THOSE MAPS THAT SHOWS ALASKA FLOATING OFF OF CALIFORNIA. AS A FAREWELL GIFT TO DAILY NEWS READERS, I OFFER THIS CARTOGRAPHIC CORRECTION.
Alaska Hepatitis B Program

- 1978: Establishment of a registry of persons found to be HBsAg-positive
- AN Hepatitis B Control Program: 1983-87: 53,000 Alaska Natives screened and 40,000 susceptible were vaccinated plus universal newborn vaccination

Lancet, 1987; 330:1134-1136
Incidence Symptomatic Hepatitis B in Alaska Native Peoples 1981-2008

- CDC/HIS Vaccine Demonstration Program begins in 16 villages of Yukon Kuskokwim Delta
- Statewide Program begins-all susceptibles immunized
  - pregnant women screened/infants HBvax + HBIG
  - begin universal newborns immunization
Age-specific Prevalence of HBV Infection
Bristol Bay Eskimos, 1994

- Anti-HBc (+)
- HBsAg (+)

Routine Infant Immunization

Positive (%) vs. Age (years)

J Infect Dis 2000;181:413-418
HCC in Alaska Natives <20 years of age

Annual Rate per 100,000

P value for trend = 0.002
The Chronic HBV Alaska Cohort

- 1560 HBsAg-positive chronically infected persons were found: population-based cohort
- All clinical and lab data computerized
- Median follow-up of cohort: 21 years
- Median age at entry: 20 years
- Median age at last follow-up: 41 years
- Five HBV genotypes: 6 sub-types found
- Over 20,000 stored sera on cohort
- Computerized program to send letters to patients every 6 months
ANTHC Program to Follow Hepatitis B Carriers

• Reminder Letter every 6 months to patient;
• Lists of patients to draw blood on goes to CHAP, Regional Hospital and provider
• Blood drawn by CHAP or hospital lab, spun down and sent to ANMC lab
• ANMC tests for ALT, AST, AFP, HBeAg/anti-HBe
• Hepatitis B RN and Brian McMahon check all results on computer weekly (about 2 hours)
• If initial ALT, AST and AFP WNL computer generated letter sent to patient informing them of normal results.
ANTHC Program to Follow Hepatitis B Carriers Continued

• If ALT or AST > UNL: Patient evaluation
  – HBV DNA level
  – History including medication use, history recent Alcohol use, history diabetes or elevated cholesterol or triglycerides
  – BMI: Need height and weight to calculate
  – Liver panel and CBC, HCV and HDV
  – Autoimmune markers in females if HBV DNA < 2,000 IU/ml
Which Patients Receive further Evaluation?

• Persons with AFP > 10ng/ml are referred for ultrasound done at nearest hospital, reviewed by teleradiography

• Patients with elevated ALT and HBV DNA > 2,000 IU/ml are recommended for a liver biopsy at ANMC to see if they need treatment

• Patients with moderate or severe inflammation or fibrosis > Metavir 2 treated
HBV Genotypes in Alaska Natives

- Genotype A2: 20.4%
- Genotype B6: 12.3%
- Genotype C2: 4.2%
- Genotype D2, D3: 6.7%
- Genotype F1: 56.4%
Geographic Distribution of HBV Genotypes in Alaska Natives
### Median Age of HBeAg Seroconversion by Genotype: Median 21 Years Follow-up*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. HBeAg+</th>
<th>Age 50% lost HBeAg</th>
<th>Age 75% lost HBeAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₂</td>
<td>34</td>
<td>19.8</td>
<td>32.1</td>
</tr>
<tr>
<td>B₆</td>
<td>6</td>
<td>19.5</td>
<td>27.5</td>
</tr>
<tr>
<td>C₂</td>
<td>36</td>
<td>47.8</td>
<td>58.1</td>
</tr>
<tr>
<td>D</td>
<td>305</td>
<td>18.0</td>
<td>27.3</td>
</tr>
<tr>
<td>F₁</td>
<td>126</td>
<td>16.1</td>
<td>24.5</td>
</tr>
</tbody>
</table>

*Gastroenterology 2007;133:1452-57  
*P<.001 genotype C vs. other genotypes
Characteristics of HBV Genotypes

• Genotype A2 and D associated with HCC in older persons mean age > 60 years
• Genotype C associated with:
  – HCC in middle age persons ~ age 50
  – More flares of ALT >2 X ULN
• Genotype F1 associated HCC in children and young adults; mean age 22 years
• Genotype B6: Similar to B1 Japan: no HCC or liver decompensation to date
Results of Follow-up

• 50% persistently normal ALT; 49%, one or more ALT elevations: Etiology
  – Chronic hepatitis B**  24%
  – Heavy ETOH use       28%
  – NAFLD                25%
  – Other/unknown        23%
Alaska Natives and American Indians in Alaska with Hepatitis C

- Anti-HCV positive AN/AI: 1,994
- Total number enrolled in study: 1,201
Conclusions: Epidemiology of HCV in Alaska Natives

- Prevalence of HCV within NHANES estimates for US
- Risk Factor distribution same as US
- Proportion who recovered from HCV same as NHANES study
- Genotype distribution similar to NHANES except slightly increased proportion of genotype 3
Hepatitis C Complications

- ESLD Total: 122
  - ESLD without HCC: 105
  - ESLD with HCC: 17
  - Liver transplant: 5

- HCC Total: 29
  - HCC with ESLD: 18 (3 living)
  - HCC without ESLD: 11 (5 living)

- Total All Complications: 133
What is Killing HCV Infected Patients Alaska HCV Outcome Study

- Retrospective-prospective population-based study
- 960 patients followed 1994-2005
  - 695 chronic HCV; 214 recovered (RIBA +)
  - Mean years prospectively: 7.2 years
  - Mean years retrospectively: 12.1 years

McMahon et al Gastroenterology 2010; in press
HCV Outcome Study: Initial Evaluation

• Alcohol usage measured at enrollment
  – 13% consumed $\geq 50$gms ETOH/day

• Incidence calculated per 100 person years of follow-up
  – End stage liver disease
  – Liver related death
  – HCC

• Persons with chronic HCV were compared to those who recovered.
Figure: Flow Diagram of HCV Positive Alaska Natives in Outcome Study 1992-2005

1590 Persons Anti-HCV + Result

57 Persons Deceased

9 Persons RIBA indeterminant

50 Persons Refused Study Participation

1326 Persons confirmed by RIBA/PCR

196 Persons Not RIBA/PCR confirmed

316 Persons Not Consented

960 Persons Consented into HCV Cohort

13 HBV Co-infections
28 HIV Co-infections

919 Persons in Primary Analyses

10 Persons Fluxuating HCV RNA

695 Persons Chronically Infected (HCV RNA +)

214 Persons Recovered from HCV (HCV RNA -)
## Incidence End Stage Liver Disease per 100 Person Years

<table>
<thead>
<tr>
<th>Factors</th>
<th>Chronic HCV</th>
<th>Recovered HCV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol &gt;50 gms/day</td>
<td>3.21</td>
<td>5.69</td>
<td>P=0.13</td>
</tr>
<tr>
<td>Alcohol &lt;50 gms/day</td>
<td>1.58</td>
<td>0.36</td>
<td>P=0.002</td>
</tr>
</tbody>
</table>
## Incidence Liver Related Death per 100 Person Years

<table>
<thead>
<tr>
<th>Factors</th>
<th>Chronic HCV</th>
<th>Recovered HCV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol &gt;50 gms/day</td>
<td>2.28 vs.</td>
<td>3.50</td>
<td>P=0.34</td>
</tr>
<tr>
<td>Alcohol &lt;50 gms/day</td>
<td>0.77</td>
<td>0.09</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>
Factors Associated with Developing End Stage Liver Disease in Alaska Native Persons (AN) with Chronic HCV

• Univariate Analysis
  – Heavy alcohol use \( (p = 0.004) \)
  – older age at infection \( (p < 0.001) \)
  – AFP > 8 ng/ml \( (p < 0.0001) \)
  – AST/ALT > 1 \( (p < 0.001) \)
  – HCV RNA level \( (p = 0.02) \)

• Multivariate analysis
  – older age
  – heavy alcohol use
  – genotype 3

• Not associated: anti-HBc, diabetes, sex, BMI
Mortality in Alaska Natives with HCV Infection vs. Those without

- AN persons with chronic HCV are 17 times more likely to die a liver related death than rest of the US population as a whole
- AN persons who recovered from HCV are 12 times more likely to die a liver related death than AN population
Survival Probability for free from end stage liver disease (ESLD) or liver-related death (LRD)

Predicted probabilities are calculated for a person infected with HCV at 25 years of age.
Difficulties in Treating HCV in Developed Countries

- Many patients are difficult to reach
- Many have medical or psychiatric contraindications
- Bottom line: > 50% of HCV infected patients will be difficult to treat even with universal health care and addition of newer medications
HEPATITIS C TREATMENT ELIGIBILITY STUDY

• Aim of Study
• To examine treatment barriers for Alaska Natives with chronic hepatitis C virus (HCV) infection
### 2003 Results:
**Reasons not treated (n = 90)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not keep appointments</td>
<td>32 (35.6%)</td>
</tr>
<tr>
<td>Alcohol or drug abuse within 6 months</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Patient decision to defer treatment</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Liver biopsy without fibrosis or normal ALT</td>
<td>8 (8.5%)</td>
</tr>
<tr>
<td>Psychiatric condition</td>
<td>7 (7.4%)</td>
</tr>
<tr>
<td>Concurrent medical condition</td>
<td>6 (6.4%)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>2 (2.2%)</td>
</tr>
</tbody>
</table>
Intervention Between 2003 and 2009

• Developed computerized program to send letters to all persons who were:
  – HCV RNA positive
    • In our consented cohort
    • Not in our consented cohort
    • Anti-HCV-positive but not ever tested for HCV RNA
## 2007 Results:
### Reasons not treated (n = 132)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient decision to defer treatment</td>
<td>36 (27.3%)</td>
</tr>
<tr>
<td>Alcohol or drug abuse within 6 months</td>
<td>29 (22%)</td>
</tr>
<tr>
<td>Did not keep appointments</td>
<td>24 (18.2%)</td>
</tr>
<tr>
<td>Concurrent medical condition</td>
<td>12 (9.1%)</td>
</tr>
<tr>
<td>Psychiatric condition</td>
<td>9 (6.8%)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Considering treatment/treatment planned</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Liver biopsy without fibrosis or normal ALT</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>Cleveland</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Patients</td>
<td>293</td>
</tr>
<tr>
<td>Not adhere</td>
<td>37%</td>
</tr>
<tr>
<td>Contraindication</td>
<td>34%</td>
</tr>
<tr>
<td>Drug use</td>
<td>13%</td>
</tr>
<tr>
<td>Defer Rx</td>
<td>11%</td>
</tr>
<tr>
<td>LFT WNL</td>
<td>5%</td>
</tr>
<tr>
<td>No. (%) Rx</td>
<td>83 (28%)</td>
</tr>
</tbody>
</table>
## TREATMENT OUTCOMES

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treated</th>
<th>Discontinued *</th>
<th>Failed</th>
<th>Relapsed</th>
<th>Responded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>20 (59%)</td>
<td>7</td>
<td>1</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>5 (24%)</td>
<td>2</td>
<td>1</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>5 (33%)</td>
<td>3</td>
<td>0</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>30 (43%)</td>
<td>12</td>
<td>2</td>
<td>26 (37%)</td>
</tr>
</tbody>
</table>

* P = 0.01 for discontinuation rate of genotype 1 versus 2&3 combined
TREATMENT IN THE REAL WORLD

• Few patients actually complete treatment
• Veterans Administration Study (2009)
  Total patients with HCV Infection: 134,000
  Completed treatment: 2,394/10,641 (22.5%)
  Per cent of total cohort completed: 1.7%

Butt et al. Liver International 2010. On line before publication
Conclusions: Large Barriers to Treatment of HCV in Developed Nations

- Access to care in US
- Able to afford treatment in US
- Eligible for treatment (25%-50%)
- Eligible and want treatment (5%-15%)
- Finish treatment (25%-70%)
- Treated and get cured (~50%)
Hepatitis C Drug Development: 2008

On Market
- Ribavirin
- IFN & PEG IFN

Phase 3
- Thymalfasin
- Albumin-IFN alfa
- Telaprevir
- Viramidine
- Boceprevir

Phase 2
- Debio25
- ME-3738
- R1728
- KPE02001003
- oglutafide
- celsosivir
- TCM-700C
- TMC 435350
- SCV-07
- PYN-17
- Silibinin
- Medusa IFN

Phase 1
- CYT 107
- VCH-759
- EMZ702
- IPH-1101
- BIT225
- BMS-790052
- ME-3738
- BI-201335
- GS9190
- JTK-652
- MK7009
- MK-3281
- BMS-791325
- VCH-916
- VBY-376
- IL-29
- Ana598
- Amarillo
- Belerofon
- EGS21
- interferons
- ribavirins
- protease inhibitors
- polymerase inhib.
- immunomodulators
- others

Research/Preclinical
- Many others including Immune stimulants
  Gene therapy

Note: Not a complete list of products in development!

McHutchinson/Pawlotsky

• 2010: Treat persons with HCV genotypes 2 & 3 and selected persons with genotype 1 with advanced fibrosis

• 2010-2013: Treat person with genotype 1 with grade 3-4 fibrosis with Peg-IFN, RBV + Protease Inhibitor

• 2014-2015 and beyond: Treat all eligible patients with all oral IFN-free regimen