Solving the dilemma of anti-HCV therapy in HCV patients with normal ALT

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Should we treat HCV Carriers with normal ALT levels?

**WHY** should we treat HCV-PNALT?

**WHO** should be treated?

**WHICH** treatment should be prescribed?

**WHEN** to start treatment?

**WHAT** should be explained to HCV carriers?

First International Course of Translational Hepatology, Florence, 2011
Patients with PNALT should not be treated
(NIH Consensus Conference, 1997; EASL Consensus Conference, 1999)

At present, it is NOT recommended that HCV carriers with PNALT undergo therapy in clinical practice because of:

1. Normal liver or mild disease in the majority of them
2. Low risk of progression
3. Uncertain response to therapy (SVR < 20%)
4. IFN-related worsening of liver disease (ALT flares) in up to 50% of the cases

Thus, these people should be followed up every 4-6 months or entered clinical trials.
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Fibrosis in HCV carriers with PNAL and in patients with abnormal ALT values

Fibrosis score (METAVIR)

- Normal ALT (n=66)
- Elevated ALT (n=798)
Progression of Fibrosis in Chronic Hepatitis C

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Conclusions: The best predictors of fibrosis progression in CHC are the extent of serum aminotransferase elevations and the degree of hepatocellular necrosis and inflammation on liver biopsy. These findings support the recommendation that patients with normal aminotransferase levels and mild liver histology can safely defer treatment.

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HCV carriers with persistently normal aminotransferase levels: normal does not always mean healthy

Claudio Puoti*
Liver Histology among 159 HCV carriers with PNAL

The Italian Study of the Asymptomatic C Carrier (ISACC)

PNAL = 9 normal values / 18 months

“Healthy carriers”

Liver damage: 83%

- Normal Liver
- Minimal CH
- Mild CH
- Moderate/Severe CH
- Cirrhosis

Puoti et al, J Hepatol 2002

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## ALT Flare in HCV Carriers with Initially ($\geq 6$ mo) Normal ALT

<table>
<thead>
<tr>
<th>Author</th>
<th>N° cases</th>
<th>FU (yrs)</th>
<th>% ALT flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persico et al, 2000</td>
<td>37</td>
<td>4.1</td>
<td>23 %</td>
</tr>
<tr>
<td>Martinot-Peignoux et al, 2001</td>
<td>24</td>
<td>3.5</td>
<td>21 %</td>
</tr>
<tr>
<td>Tsuy et al, 2001</td>
<td>120</td>
<td>3.6</td>
<td>23.3 %</td>
</tr>
<tr>
<td>Puoti et al, 2002</td>
<td>880</td>
<td>1.8</td>
<td>21.5 %</td>
</tr>
<tr>
<td>Hui et al, 2003</td>
<td>40</td>
<td>6.3</td>
<td>27.5 %</td>
</tr>
<tr>
<td>Boccato et al, 2004</td>
<td>45</td>
<td>7.3</td>
<td>33 %</td>
</tr>
<tr>
<td>Rumi et al, 2005</td>
<td>206</td>
<td>1.5</td>
<td>18.4%</td>
</tr>
</tbody>
</table>
Is fibrosis in HCV Carriers with PNAL always not progressive?

**Initial Biopsy**

- F0: 85%
- F1: 15%

**Final Biopsy**

- F0: 11%
- F1: 81%
- F2: 8%
- F3: 20%
- F4: 10%

6 - 7 yrs

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**Occurrence of hepatocellular carcinoma in an apparently ‘healthy’ HCV patient**

Claudio Puoti, Lia Bellis, Francesca Martellino, Laura Durola, Lucia Spilabotti, Orlando Dell’Unto, Alessandra Galossi and Riccardo Guarisco, Department of Hepatology and Internal Medicine, Marino Hospital, Rome, Italy.

First International Course of Translational Hepatology, Florence, 2011
Impact of Steatosis on Progression of Fibrosis in Patients With Mild Hepatitis C

Fartoux Hepatology 2005

Fig. 2. Cumulative probability of progression of fibrosis according to the percentage of steatosis at initial liver biopsy.
Peginterferon alfa-2a (180 µg qw) plus ribavirin (800 mg qd)

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CLINICAL STUDIES

Predicting efficacy and safety outcomes in patients with hepatitis C virus genotype 1 and persistently ‘normal’ alanine aminotransferase levels treated with peginterferon α-2a (40KD) plus ribavirin

Eric Snoeck¹, Stephanos J. Hadziyannis², Claudio Puoti³, Mark G. Swain⁴, Thomas Berg⁵, Patrick Marcellin⁶, Jean-Pierre Zarski⁷, Karin Jorga⁸ and Stefan Zeuzem⁹

Fig. 1 - Predicting SVR by GAM (generalised additive models) in HCV-1 patients with PNALT treated with 1200 mg of RBV
Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with peginterferonα-2a and ribavirin: a multicentric study

Claudio Puoti¹, Adriano M. Pellicelli², Mario Romano³, Fabrizio Mecenate⁴, Riccardo Guarisco¹, Giorgio Barbarini⁵, Ettore Mazzoni⁶, Lucia Spilabotti¹, Lia Bellis¹, Federica Paglia¹, Angelo Barlattani⁷, Antonio Picardi⁸, Amerigo Paffetti⁹, Maria Elena Bonaventura¹⁰, Lorenzo Nosotti¹¹, Olga Mitidieri¹², Orlando Dell’ Unto¹, Roberto Villani², Chiara Dell’ Unto¹, Aldo Morrone¹³ and Fabrizio Soccorsi², on behalf of the Club EpatoLogic Ospedaliero (Hospital Liver Club – CLEO)

First International Course of Translational Hepatology, Florence, 2011
Rates of SVR according to the presence or absence of RVR in HCV-1

Puoti et al JVH 2010
Rates of SVR according to the presence or absence of RVR in HCV-2

61 pts

RVR 55/61 (90%)

NO RVR 6/61 (10%)

SVR 54/55 (98%) NO SVR 1/55 (2%)

SVR 5/6 (83%) NO SVR 1/6

SVR 59/61 (97%) NO SVR 2/61 (3%)

Puoti et al JVH 2010

First International Course of Translational Hepatology, Florence, 2011
Predictors of SVR (univariate analysis)

Gender (female)
Baseline viral load <800,000 IU
Non-1 genotype
BMI < 24
RVR yes

Puoti C et al, Liver Int 2009
Predictors of SVR (multivariate analysis)

Gender (female)
Baseline viral load < 800,000 IU
Non-1 genotype
BMI < 24
RVR yes

Puoti C et al, Liver Int 2009
Correspondence

Sustained virological response following extremely short antiviral treatment in selected HCV carriers with persistently normal ALT

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L. Bellis

Dept of Internal Medicine and Liver Unit, Marino

We report here our experience in a very small group of HCV patients achieving sustained virological response (SVR) after an unusually short course of antiviral treatment with peginterferon (PEG-IFN) alpha-2a and ribavirin (RBV), due to early and unexpected discontinuation of therapy.
Six females HCV pos
Mean age 28±3 years, range 18–39 years
Mean ALT 18±10 IU/L, range 12–36 IU/L
Genotype HCV-2
Mean HCV RNA 210×10^3 IU/mL

Bx 3/6 (2 normal liver, 1 F1)
Stiffness 4.7±2.0 kPa, range 3.0–6.1 kPa
All patients began antiviral treatment with PEG IFN alfa 2a once weekly plus RBV 800 mg/day for a scheduled period of 24 weeks.

At wk 4 all the 6 patients had RVR.

Treatment was unexpectedly discontinued shortly thereafter (mean duration $5.5 \pm 1.5$ wks, range 4–7) because of:

- psychiatric manifestations, 1;
- severe pyrexia, 1;
- fatigue and other constitutional symptoms, 2
- personal problems, 2 (loss of employment and divorce)
All patients began antiviral treatment with PEG IFN alfa 2a once weekly plus RBV 800 mg/day for a scheduled period of 24 weeks.

At wk 4 all the 6 patients had RVR.

Treatment was unexpectedly discontinued shortly thereafter (mean duration 5.5 ± 1.5 wks, range 4 – 7) because of:

- psychiatric manifestations, 1;
- severe pyrexia, 1;
- fatigue and other constitutional symptoms, 2
- personal problems, 2 (loss of employment and divorce)

HCV RNA was further determined at 12, 24 and 48 weeks from the last administration of antiviral medication, remaining negative throughout follow-up in all patients.

To date no relapse has occurred, confirming HCV eradication.
Elevation of ALT is not a requirement for therapy of CHC


Decision making should rely on **individual patient features:**

- genotype and histology
- age of the patient
- potential progression of disease
- probability of viral eradication
- co-morbid illness and co-factors
- risk of HCV transmission
- patient motivation, desire for pregnancy
- QoL and social/psychological stigma
- major concerns over infectivity

ALT levels may have less importance in deciding who should be treated

*First International Course of Translational Hepatology, Florence, 2011*
The Cost/Benefit issue

Priority needs to be defined

• It is really impossible to perform liver biopsy in all HCV patients with PNALT.

• The cost of treating all is exceedingly high.

• Cost/benefit might be particularly favourable in:
  – young, easy to treat patients (high rate of SVR with short therapy)
  – middle age patients with “significant” liver disease (at risk of developing end stage liver disease)

Puoti C, J Gastrointest Liver Dis 2007
The age issue

Younger patients:

- respond to / tolerate therapy better
- have longer life expectancy
- are often well motivated
- usually have minimal disease
- have fewer contraindications

Decision based more on expected response and motivation than on liver disease

Puoti C, Hepatology 2009
The age issue

Older patients:

• respond less well to therapy
• more frequently have significant liver disease and/or co-factors
• often have longer infection/disease duration
• may experience more side effects
• might be less motivated

Decision more based on disease

Puoti C, Hepatology 2009
Decision making should rely on individual characteristics such as genotype, histology, age, potential disease progression, the probability of viral eradication, patient motivation, the desire for pregnancy, comorbidities, co-factors, etc. (A-VI).

Antiviral treatment might be offered without the need for liver biopsy in patients with a high likelihood of achieving an SVR (e.g. an age of <50 years + easy-to-treat HCV genotype + low viral load), in the absence of any contraindication and co-factors of poor responsiveness (A-VI).

In patients aged 50–65 years, and in those with a reduced likelihood of achieving an SVR, a liver biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis (>F2) and a higher possibility of response, depending on the HCV genotype (A-VI).
Biopsy and therapy are not recommended in therapy elderly (>70 years). These patients should be recommended to adopt lifestyle changes and undergo periodic ALT determinations (D-VI). Non-invasive assessments of fibrosis can be used to detect changes over time and consequently indicate the need for biopsy or treatment on an individual patient basis. In patients not receiving antiviral treatment, periodic ALT measurements and adequate lifestyles should be recommended. In particular, overweight and the use of alcohol should be strongly discouraged.
Management of Incidental Hepatitis C Virus Infection

A 25-year-old black woman is referred to your clinic for management of an incidental positive result on a hepatitis C virus (HCV) antibody test. She had decided to donate blood because her mother had recently become ill and required a transfusion. Three weeks after her donation, she received a telephone call and was told that her donated blood could not be used because her HCV antibody test was positive. She was encouraged to see her primary care physician to determine whether anything further should be done.
Management of Incidental Hepatitis C Virus Infection

ALT 31 U/l (normal range, 7 to 52)
AST 30 U/l (normal range, 9 to 30)
WBC 2600/mmc
PLT 175,000/mmc
Hb 11.0 g/dL
HBsAb positive

HCV-1
HCV RNA 2.3 x 10^6/mL
Management of Incidental Hepatitis C Virus Infection

When the patient returns to discuss follow-up, you administer the hepatitis A vaccine and counsel her to minimize exposure to potential hepatotoxic factors such as alcohol and excessive use of acetaminophen.

In addition, which one of the following treatment options for HCV infection, any of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.
Management of Incidental Hepatitis C Virus Infection

1. Expectant management with periodic assessment of liver function.
2. Liver biopsy, with treatment based on the findings.
3. HCV therapy with peginterferon and ribavirin.
Management of Incidental Hepatitis C Virus Infection

TREATMENT OPTION 3

HCV Therapy with Peginterferon and Ribavirin

Adrian M. Di Bisceglie, M.D.
The future
... and miles to go before we sleep

1. Better tailoring to optimize therapy
2. Identifying candidates to liver biopsy
3. Role of non-invasive methods for the assessment of hepatic fibrosis
4. Shorter treatments on the basis of rapid (4\textsuperscript{th} wk) and early (12 wk) virological responses
5. Predictive value of IL28B polymorphism in PNALT
6. Impact of new therapies
Thank you for your kind attention!