Treatment and laboratory monitoring of chronic hepatitis patients in Bulgaria

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Evolution in Diagnostic and Treatment of HCV infection

- Discovery of HCV genome 1989
- Treatment with IFN alfa 3 ME s.c. 3 x weekly for 24 or 48 weeks
- IFN alfa and RBV for 24 or 48 weeks
- Peg-IFN alfa once weekly
- Peg-IFN alfa and RBV for 24 or 48 weeks
- PCR qualitative
- PCR quantitative
- bDNA
- Genotype
- RT-PCR
- Tailoring treatment
- New antiviral drugs
Definition of virological response

Reduction of HCV RNA

- ETR: SVR
- 72 weeks
- 48 weeks
- 24 weeks
- 12 weeks
- 0 weeks

- Undetected HCV RNA (<50 IU/mL)
- RVR
- cEVR
- pEVR

Treatment
## Treatment of HCV infection in Bulgaria – past and present

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoblastoid IFN-α</td>
<td>1994</td>
</tr>
<tr>
<td>Recombinant IFN-α</td>
<td>1995</td>
</tr>
<tr>
<td>Recombinant IFN-α + Ribavirin 6 months</td>
<td>1996</td>
</tr>
<tr>
<td>Recombinant IFN-α + Ribavirin 12 months</td>
<td>1998</td>
</tr>
<tr>
<td>Repeat treatment with r IFN-α + Ribavirin</td>
<td>1999</td>
</tr>
<tr>
<td>Peg-IFN α + Ribavirin for 6 or 12 months (SOC)</td>
<td>2000</td>
</tr>
<tr>
<td>Repeat treatment with Peg-IFN α + Ribavirin</td>
<td>2002</td>
</tr>
<tr>
<td>Clinical Trials: New IFNs (Locterone, Multiferon); Ribavirin analog (Viramidine); Immunomodulators</td>
<td></td>
</tr>
</tbody>
</table>
ETR and SVR in treatment of chronic HCV infection with IFNs

Distribution of HCV genotypes in Bulgarian patients with chronic HCV infection according different methods

HCV genotypes 4 and 6 were found recently.

Antonov K et al. 1998
SVR in patients with different HCV genotypes infection, treated with PEG-IFN α2a and Ribavirin

Antonov K et al. 2005
Differences in age between the patients infected with HCV genotype 1 or 3.

Antonov K et al. 2010
Differences in HCV RNA level between HCV genotype 1 and 3.

Antonov K et al. 2010
Impact of liver steatosis on SVR during treatment with Peg-IFN α2a and Ribavirin

Antonov K et al. 2009
IL28B polymorphism (rs12979860) in Bulgarian patients with chronic HCV genotype 1 infection

- TT genotype: 65.6%
- CT genotype: 18%
- CC genotype: 16.4%

Ivanova A et al. 2010
SVR and IL28B polymorphism (rs12979860) in Bulgarian patients with chronic HCV genotype 1 infection

Ivanova A et al. 2010
SVR according HCV RNA levels on the moment of EVR determination

Antonov K et al. 2005
Goals of HBV therapy

Sustained suppression of HBV replication

- Biochemical response
- Serological response
- Histological improvement

Preventing disease progression to cirrhosis, decompensated cirrhosis, HCC and death

Improve quality of life and survival

APASL Consensus. Hepatol Int. 2008
AASLD Guideline. Hepatology 2007
## Treatment of HBV infection in Bulgaria – past and present

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<th>Treatment</th>
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<tbody>
<tr>
<td>Recombinant IFN-α2a for 6 months</td>
<td>1991</td>
</tr>
<tr>
<td>Recombinant IFN-α2a for 12 months</td>
<td>1998</td>
</tr>
<tr>
<td>PEG-IFN α2a</td>
<td>2004</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>2000</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>2009</td>
</tr>
<tr>
<td>Entecavir</td>
<td>2009</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2009</td>
</tr>
<tr>
<td>Clinical Trials: Cycling treatment with IFN-α2a,</td>
<td></td>
</tr>
<tr>
<td>Cycling treatment with PEG-IFN α2a, Therapeutic</td>
<td></td>
</tr>
<tr>
<td>vaccine, Emtricitabine, Clevudine, Adefovir.</td>
<td></td>
</tr>
</tbody>
</table>
Frequency of HBeAg (-) neg. chronic hepatitis B in Bulgarian patients

Jelev D et al. 2010
6 months IFN therapy in HBeAg (-) patients

![Graph showing treatment response percentages for different IFN doses (1.5 MIU IFN, 3 MIU IFN, 9 MIU IFN, 18 MIU IFN)].

- **End of treatment**
  - 1.5 MIU IFN: 81%
  - 3 MIU IFN: 72%
  - 9 MIU IFN: 90%
  - 18 MIU IFN: 54%

- **Sustained response**
  - 1.5 MIU IFN: 12%
  - 3 MIU IFN: 11%
  - 9 MIU IFN: 10%
  - 18 MIU IFN: 5%

Krastev Z et al. 1998
12 months Peg-IFN or IFN therapy in HBeAg (+) patients

Jelev D et al. 2008
12 months Peg-IFN or IFN therapy in HBeAg (-) patients

Jelev D et al. 2008
HBV genotypes in Bulgarian patients with acute and chronic hepatitis B

- Genotype A: 17.3%
- Genotype D: 80.2%
- Mix genotype: 2.5%

ALT > 4x ULN and HBV DNA < 50 000 000 copies/ml is associated with ETR in > 90% of pts.

Jelev D et al. 2008
Intermittent 1.5 MIU IFN Treatment

7/37, 19% Non-Responders

30/37, 81% Responders were randomized

GROUP A
Received Intermittent low-dose IFN therapy

GROUP B
Control group: no further therapy

Initial treatment with IFN

Krastev Z et al. J Hepatology 2005
Rate of Relapses in Cyclically treated and Non-cyclically treated Patients

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 months after the initial successful treatment with 1,5 MIU IFN

Group A
Group B

p < 0.05

End of cyclic IFN therapy

p < 0.01

Krastev Z et al., J Hepatology 2005
Intermittent Peg IFN α2a treatment
24 months post initial therapy

Initial 12-mo IFN course

Rest period 3 months

Start of cyclic therapy with Peg IFN 135 mcg

Peg IFN 135 mcg/wk for 3 months

Rest period 3 months

The cycle was repeated 4 times

Cyclic therapy relapsers 38%

Control group relapsers 63%
HBsAg and HBV DNA during cyclic therapy with 135 mcg Peg IFN α2a in a patient with CHB

Jelev D et al. 2010
Disappearance of HBV DNA and ALT normalization during 12 months therapy with Lamivudine

HBsAg (+) patients

HBsAg (-) patients

Jelev D et al. 2001
Tenofovir 4-year efficacy data (on treatment analysis of study 102 and 103)*

On/After week 72, patients with confirmed HBV DNA ≥400 copies/mL were eligible to add emtricitabine (FTC) in a fixed dose combination tablet at the discretion of investigator. 34 patients in the HBeAg(+) study and 4 patients in the HBeAg(−) study added FTC.


* Missing = Excluded
‡ Number of patients entering Year 4
Treatment of HBV (+) pos. decompensate liver cirrhosis with Lamivudine resistance

Krastev Z et al. 2009
Treatment of HDV infection in Bulgaria – past and present

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant IFN α2b 10 MU 3 x/ week for 12 months</td>
<td>1991</td>
</tr>
<tr>
<td>Recombinant IFN α2a 6 MU 3 x/ week for 12 months</td>
<td>1994</td>
</tr>
<tr>
<td>Repeat treatment with recombinant IFN α2a for 12 months</td>
<td>1996</td>
</tr>
</tbody>
</table>
Median HDV RNA (pg/mL) over time

Undetectable HDV RNA: ETR - 18%; 12 months later - 12%

Antonov K. 1997
Median ALT (U/l) over time

Normal ALT: End of therapy – 41%; 12 months later – 24%

Antonov K. 1997

42 U/l (up normal limit)
Conclusion

- The combined PEG-IFN and Ribavirin therapy for chronic HCV infection in Bulgaria is highly effective as a result of good patient's selection.

- The results of IFN therapy in Bulgarian patients with chronic HBV infection are quite disappointing because of common infection with HBV genotype D.

- Cyclic IFN therapy is effective to keep on the achieved viral response in patients with chronic HBV infection.
Conclusion

- Nucleos(t)ide analogs suppress HBV replication and improve liver disease.

- In HBeAg (+) pos. patients HBsAg loss and anti-HBs seroconversion can be observed during the nucleotide therapy.

- The duration of nucleos(t)ide analogs therapy is still open question.

- IFN therapy improves liver disease and suppress HDV replication in patients with chronic HDV infection but new therapeutic strategy is needed.