A NEW ERA FOR SCREENING AND TREATMENT OF HEPATITIS C: A PUBLIC HEALTH CHALLENGE

VIRAL HEPATITIS: CROATIAN CONSENSUS CONFERENCE 2013

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1998: HBV vaccination at the age of 12
2007: universal vaccination
2007: PEG IFN for all G
2007: ELPA’s Declaration on hepatitis C in EUP
2008: initiation at first round table
2009: CRO Parliament Resolution on Viral Hepatitis
2012: PI registration; first experience with triple/name based patient; working group for national Hepatitis plan formed
2013: January - WG mtg; February - consensus conference; PI reimbursement

New discoveries led to consensus conference 2013 in Zagreb.
Presentation about new knowledge about:

- Epidemiology
- Serological and molecular diagnostic
- Determining polymorphism of promoter gene for IL-28
- Assessment of the stage of fibrosis
- Monitoring of patients with viral hepatitis
- Treatment of chronic hepatitis C (genotypes 1-6)
- Treatment of special populations (children, patients on dialysis, transplants’ patients, people with HIV/HCV co-infection)
- Side effects of treatment
Low prevalence in Croatia
Prevalence of anti-HCV in IVDU 30-50%
Incidence new anti-HCV 2000-2007 was 400 persons/year declining after 2008
35,000-45,000 people living with CHC (seroprevalence anti-HCV ab in subgroups)
Testing for HCV - determining specific antibody enzymes
  - immuno-tests
  - *point-of-care (POC)* tests
If positive → HCV RNA or viral capsid antigen
PCR detection and quantification of HCV RNA - method of choice

Patients treated with protease inhibitors on who individual approach to treatment is applied, determination of viral kinetics is based on molecular tests with LLOQ ≤ 25 IU/mL and LLOD in the range of 10-15 IU/ml.

It is recommended to use molecular tests with identical LLOD and LLOQ in the monitoring of viral kinetics during triple therapy.
2.2. Determining Promoter Gene Polymorphism in IL-28B

- IL-28B genotyping is recommended in pre-therapy treatment of patients with CHC
- IL-28B is important diagnostic tool in CHC naive patients doubt between dual vs. triple therapy
- Biological and clinical significance of IL-28B genotype proven in patients with HIV/HCV co-infection
2. Diagnosis

2.3. Assessment of the Stage of Fibrosis

- Fibrosis stage for all patients in the pre-treatment
  - Liver biopsy
  - Non-invasive

- METAVIR

- Biopsy not necessary in G2/G3 and in G1 naive when triple is planned

- For noninvasive - elastography + serologic (APRI or Fibrotest)

- TE can be considered reliable in patients with ALT values elevated up to 3x above normal limits
Regular monitoring of all patients with chronic viral hepatitis

- monitoring of patients involves biochemical (ALT) and molecular evaluation of the response as well as the occurrence and classification of side effects
- Same test and preferably in the same laboratory
- CHC patients in the stage of liver cirrhosis should be continuously monitored in order to timely assess decompensation of main disease or the development of HCC
Therapy is recommended for patients:
- 1) With acute infection
- 2) with increased levels of ALT
- 3) with normal ALT and F ≥ 2 (METAVIR) or equivalent non-invasive methods of assessing liver fibrosis;
- 4) previous non responders and relapsers G1
- 5) with compensated liver cirrhosis and
- 6) on chronic hemodialysis program

3.2.2. Therapy is indicated for patients:
- 1) with severe extrahepatic manifestations of HCV infection
- 2) with HBV co-infection
- 3) with HIV co-infection
- 4) after a minimum of 6 months of abstinence from alcohol or i/v drug using with / without substitution therapy and
- 5) with liver transplant

3.2.3. Therapy is not recommended for patients with
- 1) with fulminant hepatitis;
- 2) with normal ALT without presence of fibrosis;
- 3) with a transplanted kidney and
- 4) pregnancy
Treatment with pegylated interferon alfa-2a/2b for 24 weeks if HCV RNA was detectable in the serum for longer than 12 weeks from the onset (first occurrence of elevated aminotransferases)
VIRAL HEPATITIS (FOCUS ON HCV)  
CROATIAN CONSENSUS CONFERENCE  
4. THERAPY  
4.2.1. CHRONIC HEPATITIS C G 1

- Significant changes in the treatment of patients with CHC according to the guidelines from 2009
- G1- first generation protease inhibitors
  - Boceprevir
  - Telaprevir
- with PEG IFN (afla2a/2b) and RIBA
Treatment of naive CHC G1 patients must be based on an analysis of the fibrosis stage (biopsy or elastography), IL-28 genotype rapid viral response (RVR) and the patient's age.

For patients with F1 (Metavir) or Fibroscan <7.5 kPa, dual therapy or to wait for more effective drugs.

F2 or Fibroscan 7.5-9.5 kPa - dual therapy. However, in patients with a combination of adverse predictors of treatment outcome (> 40 years, non-CC genotype for IL-28B and without RVR-a), it is recommended to continue treatment with triple therapy.

F3 and F4 or Fibroscan > 9.5 kPa - triple therapy.
In taking decision for non naive patients with CHC G1 - take into account
- Type of virological response to prior treatment
- Stage of fibrosis
a. For patients with previous relapse triple therapy is recommended

- In *relapsers without cirrhosis* (F1-F3) recommendation to use of PEG IFN-α2a/b, ribavirin and protease inhibitors (boceprevir 4+32+12 weeks or telaprevir 12+12*+24 weeks). Relapsers therapy with telaprevir who achieve eRVR lasts in total 24 weeks, so in these patients shortened protocol can be applied

- In *relapsers with cirrhosis* (F4) triple therapy is also recommended i.e. boceprevir scheme 4+44 weeks or telaprevir 12+36 weeks
b. In patients with partial response, the decision on the treatment depends on the stage of fibrosis

- For patients with F1 (Fibroscan <7.5 kPa), it is recommended to wait for more effective drugs
- For patients with F2 and F3 (Fibroscan > 7.5 kPa), it is recommended to use triple therapy i.e. to use boceprevir (4 +32 +12 weeks) or telaprevir (12 +36 weeks)
- For patients with compensated cirrhosis (F4) triple therapy with boceprevir (4 +44 weeks) or telaprevir (12 +36 weeks) is recommended
c. For null-responders - wait for more effective drugs

- F3 and F4, (Fibroscan > 9.5 kPa), we can consider initiating treatment with a *lead-in phase*

- If viremia reduction > 1 log 10 IU/mL during *the lead-in phase*, it is recommended to continue triple therapy i.e. boceprevir (4 +44 weeks) or telaprevir (12 +36 weeks)

- If viremia reduction during *the lead-in phase* was <1 log10 IU HCV RNA - terminate the therapy
d. *unknown virological response* - consider treatment with a lead-in phase (as in null responders)

- *unknown response and cirrhosis* - triple
PEG/RBV = SOC for newly diagnosed non-G 1

RGT is recommended (lack of more effective treatment for CHC patients with non-G 1 infection)

Protocol and the length of treatment of naive CHC patients - determined depending on the genotype infection, IL28B genotype, basal viremia, stage of fibrosis and viremia kinetics during the treatment
Depending on the basal viremia:

- **low viremia** (<600,000 IU / ml) = PEG-IFN alpha 2 and RBV during 16 weeks if RVR was achieved. If HCV RNA is still present in 4th week of treatment - the treatment shall be administered 24 weeks.

- **high viremia** (> 600,000 IU / ml) = PEG-IFN alpha 2 and RBV for 24 weeks if RVR was achieved. If RVR, or cEVRI, or pEVR or DVR were not achieved - treatment is to be terminated after 24 weeks.
PEG-IFN alpha 2 and RBV during 24 weeks

If no RVR but pRVR - 48 weeks but only if there is DVR and cc IL28B

If no RVR nor cEVR nor pEVR nor DVR - stop at 24 weeks
regardless of basal viraemia = PEG/RBV for 48 weeks with achieved cEVR or pEVR (with DVR).

- If there is no DVR treatment terminates after 24 weeks.
regardless of the stage of fibrosis or basal viraemia = PEG-IFN /RBV for 48 weeks if cEVR is achieved.

- If pEVR is achieved - DVR also has to be achieved otherwise treatment terminates after 24 weeks.
Children with CHC:

- older than 3 years in the case of significant fibrosis
- Recommended - PEG IFNα2b /RBV
- For G2 and G3 anticipated duration of treatment is 24 weeks, for G1 and G4 48 weeks
test for HCV and HBV

Consider benefits - risks of therapy (expected lifespan, comorbidities, and the possibility of kidney transplantation)

CHC positive patients with a transplanted kidney should be treated with interferon only if benefits of this therapy significantly increase the risk of kidney rejection.
Reinfection with HCV occurs in almost all patients with measurable viremia at the time of transplantation.

Four antiviral treatment strategies are proposed:
1. pre-transplant antiviral therapy
2. post-transplant prophylactic antiviral therapy
3. preemptive therapy in the early post-transplant period
4. post-transplantation antiviral therapy for those to whom hepatitis is histologically confirmed
measurable viremia - candidate for treatment

carefully evaluate toxicity (DDI)
regularly monitoring (at least once monthly)
- PEG IFN-α2 and ribavirin doses reduction
- if ribavirin is stopped for seven or more days - PI should also be interrupted
- “all or nothing” PI dose - apply in full dose or terminate application
- In case of anemia reduce doses of ribavirin in patients with hemoglobin <10 g/dl
- Usage of erythropoietin may be justified in order to prevent interruption of therapy