Viral Hepatitis Prevention Board

Techinical Meeting

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

VIRAL HEPATITIS: CROATIAN CONSENSUS CONFERENCE 2013

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A LITTLE BIT OF HISTORY

- 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

VIRAL HEPATITIS
CROATIAN CONSENSUS CONFERENCES

- Croatian consensus conference about viral hepatitis; 2005. and 2009.
- New discoveries led to consensus conference 2013 in Zagreb.

VIRAL HEPATITIS (FOCUS ON HCV) CROATIAN CONSENSUS CONFERENCE *CONTENT:*

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

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1. EPIDEMIOLOGY:

- 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)

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2. DIAGNOSIS

2.1. SEROLOGICAL AND MOLECULAR DIAGNOSTIC

- 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

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2. DIAGNOSIS

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

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2. DIAGNOSIS
2.3. ASSESMENT 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

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3. MONITORING OF PATIENTS WITH VIRAL HEPATITIS

- 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

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4. THERAPY

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) pregnance

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4. THERAPY

4.1. ACUTE HEPATITIS C

- 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)

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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

VIRAL HEPATITIS (FOCUS ON HCV) CROATIAN CONSENSUS CONFERENCE 4. THERAPY 4.2.1.1. CHRONIC HEPATITIS C G 1 - NAIVE

- 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

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4. THERAPY

4.2.1.2. CHRONIC HEPATITIS C G 1 – TREATMENT EXPERIENCED

- In taking decision for non naive patients with CHC G1 - take into account
  - Type of virological response to prior treatment
  - Stage of fibrosis

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4. THERAPY

4.2.1.2. CHRONIC HEPATITIS C G 1 - TREATMENT EXPERIENCED

- a. For patients with previous relapse triple therapy is recommended
  - In *relapsers without cirrhosis* (F1-F3) recommendation od 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 shorted 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

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- 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

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4. THERAPY

4.2.1.2. CHRONIC HEPATITIS C G 1 - TREATMENT EXPERIENCED PATIENTS

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

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4. THERAPY

4.2.1.2. CHRONIC HEPATITIS C G 1 - TREATMENT EXPERIENCED

d. *unknown virological response* – consider treatment with a lead-in phase (as in null responders)

- unknown response and cirrhosis - triple

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4. THERAPY
4.2.2. CHRONIC HEPATITIS C NON G 1 - (G2, G3, G4, G5, G6)

- PEG/RBV = SOC for newly diagnosed non-G 1
- RGT is recomended (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

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4. THERAPY

4.2.2.1. HCV G2 AND G3 (METAVIR F≤3; WITHOUT NEGATIVE CO-FACTORS)

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.

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4. THERAPY
4.2.2.2. HCV G2 AND G3 (METAVIR ≤3; WITH ONE OF MORE NEGATIVE CO-FACTORS)

- 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

VIRAL HEPATITIS (FOCUS ON HCV) CROATIAN CONSENSUS CONFERENCE *4. THERAPY 4.2.2.3. HCV G2 OR G3* (ISHAK F 5-6 ILI METAVIR >3)

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.

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4. THERAPY

4.2.2.4. HCV G4, G5, G6

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.

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5. SPECIAL POPULATION

5.1. CHILDREN

- 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

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5. SPECIAL POPULATION
5.2. PATIENTS ON HEMODYALISIS

- 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

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5. SPECIAL POPULATION

5.3. TRANSPLANTED PATIENTS

- 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

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5. SPECIAL POPULATION

5.4. HIV/HCV COINFECTION

- measurable viremia - candidate for treatment
- carefully evaluate toxicity (DDI)

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- 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