The Netherlands: Hepatitis C treatment guidelines

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Conflicts of interest

None
Content

Hepatitis C in the Netherlands
• Patient population
• Screening
• Dutch care
• Dutch research

Treatment of hepatitis C monoinfection in the Netherlands
• Indications and contra-indications for treatment
• Antiviral therapy for chronic hepatitis C, genotype 1
• Management of side effects
• Drug-drug interactions
Hepatitis C population

Prevalence
- Netherlands 0.1 – 0.4%
- Europe 0.4 – 4.0%

Hepatitis C population

Hepatitis C population

![Graph showing estimated number of adults living with HCV](image-url)
Genotype distribution

Genotypes in the Netherlands

- Genotype 1 (49.3%)
- Genotype 3 (29.3%)
- Genotype 4 (10.5%)
- Not known (0.9%)
- Multiple (2+4) (0.3%)
Dutch viral hepatitis program

- BIBHEP program to:
  - Increase awareness of hepatitis in GPs and specialists
  - Identify patients with chronic hepatitis B or C
  - Treat patients with chronic hepatitis B or C

- Aim is to reduce mortality of chronic hepatitis B and C

- Members: hepatitis specialists and public health specialists

- Workshops, e-learning, e-consultation, automatic alerts etc.
Dutch care for hepatitis patients

- Treatment restricted to certified viral hepatitis treatment centers
  - 45 hospitals

- Specific criteria
  - At least two hepatitis specialists of which one hepatologist
  - Experience with hepatitis B and C treatment
  - Updated about recent literature
  - Participation in multi-center trials
  - Viral diagnostics
Dutch research: VIRID

High-dose versus standard-dose weight-based ribavirin in combination with peginterferon alfa-2a for patients infected with hepatitis C virus genotype 1 or 4
Duotherapy with high dose ribavirin leads to more HCV RNA loss in the first 24 weeks, after week 24 this effect lost significance.
Dutch research: CIRA

Study on chronic Hepatitis C treatment with peg-interferonα, ribavirin and amantadine in treatment naive patients

Study design
• Randomized, double blind, placebo controlled
• 26 centres, Jan 2001 – Jul 2007
• 2 groups (n=297)
  • Standard of therapy
  • Standard of therapy with 100 mg amantadine twice daily

• Conclusion: No beneficial effects of adding amantadine to peg-interferonα-2b and ribavirin in previously untreated chronic hepatitis C patients.

Van Soest et al. Dig Liver Dis. 2010
Guidelines for HCV treatment

- Approval of Protease Inhibitors in 2012
- Indication:
  - Consider treatment in all patients with no contraindications
  - Treatment warranted in patients with fibrosis ≥ F2 (metavir)
- Contra-indications:

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>decompensated cirrhosis</td>
<td>anemia</td>
</tr>
<tr>
<td>uncontrolled depression</td>
<td>neutropenia</td>
</tr>
<tr>
<td>psychosis</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>epilepsy</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td>pregnancy</td>
<td>ongoing alcohol/drugs abuse</td>
</tr>
<tr>
<td>desire to have children</td>
<td>NR to DAA based treatment (resistance)</td>
</tr>
</tbody>
</table>

Lamers et al. Neth J Med 2013
Telaprevir regimen

Naives or relapers (both without cirrhosis)

Partial or null responders and patients with cirrhosis

HCV RNA undetectable* at week 4 and 12: stop all medication

If cirrhotic NR: consider treatment in trial (SVR ~14%)

* With a lower limit of detection of 10-15 IU/ml
Boceprevir regimen

Naives (without cirrhosis)

Relapsers or partial responders (both without cirrhosis)

Null responders and patients with cirrhosis

Week

HCV RNA determination + ‘stopping rules’

NR excluded from phase III trials

* With a lower limit of detection of 10-15 IU/ml
Side effects

Unique in our guideline is the management of side effects.

- Anemia
- Neutropenia
- Thrombocytopenia
- Rash and pruritus
- Psychiatric side effects
Management of side-effects

Anemia

- **Hb > 6.2 mmol/l**
  - When symptomatic: ribavirin dose reduction with steps of 200 mg

- **Hb ≥ 5.3 - < 6.2 mmol/l**
  - Ribavirin dose reduction with steps of 200 mg

- **Hb < 5.3 mmol/l**
  - Blood transfusion
  - Erythropoietin agents
  - Temporary discontinuation of ribavirin
  - In case of bone marrow suppression: reduce peg-IFNα
Management of side effects

Neutropenia

- Peg-interferon dose reduction:
  If $n < 0.75 \times 10^9 /l$

- Peg-interferon discontinuation:
  If $n < 0.5 \times 10^9 /l$

Thrombocytopenia

- Peg-interferon dose reduction:
  If $T < 50 \times 10^9 /l$

- Peg-interferon discontinuation:
  If $T < 25 \times 10^9 /l$
Management of side effects

Rash

- More with telaprevir
- Localization: trunk, extremities, friction sides, anal region

**Grade 1 rash**
Localized skin eruption

- Emollients in combination with class 3 topical corticosteroids
- If necessary oral anti-histamines *
- Continue telaprevir

**Grade 2 rash**
Diffuse skin eruption up to 50% of body surface

- Emollients in combination with class 3 topical corticosteroids, if necessary oral anti-histaminics
- Consultation dermatologist
- Continue telaprevir
- Close follow-up of patients, inform about systemic or alarm symptoms
Management of side effects

Grade 3 rash
- skin involvement > 50% of body surface
- or significant systemic symptoms
- or presence of: vesicles, bullae, ulceration, epidermal detachment, target lesions or palpable purpura

- Discontinue telaprevir, if no improvement within 7 days, discontinue peg-IFNα
- Consultation dermatologist

Grade 4 rash
- TEN, SJS or DRESS**

- Admission to hospital
- Consultation dermatologist
- Discontinue all drugs
Management of side effects

Psychiatric side effects:

• Consider prophylactic treatment in all patients with a history of depression or signs of depression at baseline

De Knegt et al. Aliment Pharmacol Ther 2011
Lamers et al. Neth J Med 2013
Drug-drug interactions

- Boceprevir and Telaprevir are substrates of Cytochrome P450 3A iso-enzyme and P-glycoprotein (PgP)

- Interactions suspected with inductors or inhibitors of CYP3A or PgP

- Prior to start therapy, check:
  - [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
  - Dutch handbook for drug interactions with anti-HCV infection agents
  - Consultation of pharmacist
Examples of drug-drug interaction

**Decreased concentration**
- Estrogen contraceptives
- SSRI
- Opioids/Methadon
- (HIV protease inhibitors)

**Increased concentration**
- Lipid lowering drugs
- Calcium channel blockers
- Anti-mycotics
- Clarithromycin
- Benzodiazepines
- Digoxin
- Immunosuppression:
  - Tacrolimus
  - Prednisone

**Changed PI concentration**
- Rifampicine
- Anti-mycotics
Viral Hepatitis Prevention Board Meeting
November 2013

The Netherlands: Hepatitis C treatment guidelines

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Indications for treatment

• Treatment should be considered in all patients who do not have contraindications for treatment
• Fibrosis assessment is important
  • F0-1: treatment can be postponed, watchful waiting
  • F2: treatment should be strongly considered
  • F3-4: treatment, unless contraindications

• Subgroups with limited benefits:
  • Elderly patients (>70 years)
  • Patients with (longstanding) asymptomatic disease and low stage of fibrosis (Metavir F ≤ F2)
Acute hepatitis C

- Populations: mainly HIV co-infected homosexual patients
- Treatment if HCV RNA is still positive at 3 months after exposure
- Aim: to prevent chronic HCV infection
- Treatment with Peginterferon alfa monotherapy for 24 weeks
  Ribavirin no proven benefit
- SVR > 90%
Resistance

• Boceprevir and Telaprevir are highly specific inhibitors of viral NS3/4A serine protease.

• One or two mutations in protease can be sufficient for viral failure due to resistance -> no monotherapy

• Resistance
  - If virological failure, than 80% resistance, mainly G1a
  - Stopping rules should be followed strictly to prevent protease inh resistance in the future
  - No strict indication for determination of antiviral resistance at the moment, no consequences, but biobanking is usefull for the future
Virological response

Baseline Behandeling

Non-responder

Partial responder

Relapser

Breakthrough

HCV RNA

Ondetecteerbaar HCV RNA

Tijd

6 maanden

Antiviral treatment for HCV genotype 1

• Treatment regimen:
  • **PR:**
    Peg-interferonα-2a 180 µg/wk + weight based ribavirin (1000–1200 mg)
    OR
    Peg-interferonα-2b 1,5 µg/kg/wk + weight based ribavirin (800–1400 mg)
    
    WITH

• Protease Inhibitor (PI)
  Telaprevir 750 mg three times daily
  OR
  Boceprevir 800 mg three times daily
Differences Telaprevir and Boceprevir

- **Telaprevir**
  - No lead-in
  - RGT for treatment naive and relapse patients
  - Duration RGT: 24 weeks
  - 3 stopmoments: week 4, 12 and 24
  - Intake with 20 g fat containing food

- **Boceprevir**
  - 4-week lead-in
  - RGT only for treatment naive patients
  - Duration RGT 28 weeks
  - 2 stopmoments: week 12 and 24
  - Intake with small meal
Predictors of response

- Previous treatment results
- Low fibrosis stage ($\leq F2$)
- On-treatment decline of HCV RNA
- Viral subtype 1b
- Low baseline viral load
- Young age
- Non-black race
Treatment naïve HCV G1 patients

- T + PR: 69-75%
- B + PR: 63-66%
- PR: 38-44%
Treatment experienced HCV G1 patients

Cirrhotic NR:

SVR ~ 14%, so consider clinical trial
## Side effects

<table>
<thead>
<tr>
<th>Peginterferon/Ribavirin</th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Anemia</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>Neutropenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Pruritus</td>
<td>(anal) Pruritus</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>Rash</td>
<td>Dysguesia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Telaprevir rash

Grade 1

Grade 2
Antiviral therapy for HCV G2,3

PR: Peg-interferonα-2a or -2b AND 800 mg Ribavirin

Week 4

- HCV RNA negative
- HCV RNA positive

24 weeks treatment, in case of severe side effects consider 16 weeks of therapy

No negative prognostic factors
Presence of negative prognostic factors

24 weeks treatment
48 weeks treatment
Antiviral therapy for HCV G4,5,6

**PR:** Peg-interferonα-2a or -2b AND weight-based Ribavirin

- **Week 4**
  - HCV RNA negative → 24 weeks treatment in case of favorable prognostic factors
  - HCV RNA positive or absence of favorable prognostic factors
    - **Week 12**
      - $< 2 \log_{10}$ decline in HCV RNA → Stop treatment
      - HCV RNA negative or $\geq 2 \log_{10}$ decline in HCV RNA
        - **Week 24**
          - HCV RNA positive → Stop treatment
          - HCV RNA negative → Continue treatment until week 48
        - Determine HCV RNA at 24 weeks treatment
Impaired renal function: DAA and Ribavirin

(not mentioned in guideline)

PAN study: noninterventional study

895 patients: 575 Telaprevir
211 Boceprevir
109 Dual therapy

• Wk 12 of treatment
  • 5.5 % had decreased renal function to < 60 ml/min
  • More frequent in Telaprevir/Boceprevir than Dual therapy (p< )
  • Associated factors: age, arterial hypertension, DM, higher baseline creatinine, being on triple therapy
  • More pronounced anemia, likely caused by accumulation of ribavirin due to an impaired renal elimination

Mauss et al. Hepatology 2013
TPR BID

(not mentioned in guideline)
Optimize study:
• Randomized, multicenter, open label
• Non-inferiority: telaprevir TID or BID
• Treatment naive patients

• SVR 12, safety/tolerability comparable

Buti et al. AASLD 2012
**VIRID: Anemia management**

### Table: Dose adjustment rules

<table>
<thead>
<tr>
<th>Anemia</th>
<th>PEG-IFN</th>
<th>Ribavirin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt; 6.8 mmol/l</td>
<td></td>
<td></td>
<td>Erythropoietin*</td>
</tr>
<tr>
<td>Hb &lt; 5.0 mmol/l</td>
<td></td>
<td>A level reduction**</td>
<td>Transfusion &amp; erythropoietin*</td>
</tr>
<tr>
<td>Hb &lt; 4.0 mmol/l (NCI toxicity grade 4)</td>
<td></td>
<td>Discontinue ribavirin***</td>
<td>Transfusion &amp; erythropoietin*</td>
</tr>
</tbody>
</table>
VIRID: Results anemia

![Graph showing Hb levels over weeks for high and standard dose ribavirin](image)

Table 3. Safety: on treatment hematotoxicity and intervention

<table>
<thead>
<tr>
<th></th>
<th>High dose ribavirin (N=52)</th>
<th>Standard dose ribavirin (N=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt;6.8 mmol/l</td>
<td>39 (75.0%)</td>
<td>27 (48.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hb &lt;5.0 mmol/l</td>
<td>9 (17.3%)</td>
<td>1 (1.7%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hb &lt;4.0 mmol/l</td>
<td>1 (1.9%)</td>
<td>0 (0.0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Epoetin use</td>
<td>39 (75.0%)</td>
<td>24 (41.4%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Transfusion</td>
<td>8 (15.4%)</td>
<td>1 (1.7%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Ribavirin dose reduction</td>
<td>16 (30.8%)</td>
<td>9 (15.5%)</td>
<td>0.057</td>
</tr>
</tbody>
</table>
Follow up after treatment

• HCV RNA testing 24 weeks after end of treatment

• Hypothyroidism can arise during treatment until 2 years after treatment, so assess thyroid function

• Cirrhotic patients should be assessed in a viral hepatitis centre due to the risk complications of cirrhosis and development of HCC