CLINICAL ASPECTS OF TREATMENT IN CHRONIC HEPATITS C– MONITORING, COMPLICATIONES , DRUG INTERACTIONES

PARTICULARITIES IN RISC CATEGORIES OF PATIENTS IN ROMANIA

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Summary:

1. Tipes of treatment
2. Initiation criteria for treatment
3. Monitorization and adverse events
4. Drug interactions
5. Specific issues related to the patients from risk categories with chronic VHC infection, in Romania

Information above is conform to the last Treatment guide from the (NHIH) National Health Insurance House (2015- 2016)

New treatment guides are expected in the next few months.

Types of treatment:

1. Treatment cu PEGylated interferon: ~ 50% efficient→ ~ 70% efficient (tri-therapy)

In Romania: **treatment with tri- therapy including PEGylated interferon were not available from Romanian Health Insurance System**

2. Treatament interferon –free, antiviral direct (>95% efficient and evident clinical advantage).

In Romania: **Ombitasvirum+ Paritaprevirum+ Ritonavirum (Viekirax) + Dasabuvirum (Exviera)**

In "Victor Babes" Clinical Hospital of Infectious and Tropical Diseases we also had research projects and clinical trials involving this antiviral molecules all along this period of time while standard of care for chronic hepatitis C changed to oral therapy.

Clinical an virusological criteria for specific* treatment initiation:

Primary criteria for treatment inititation:

- hepatic fibrosis stage (was the criteria that determined the type of treatment in the last National Guide of treatment, from 2 available options- see slide 2);
- presence/absence of systemic VHC DNA.

Secondary criteria for treatment inititation :

- previous treatment status of the patient (naiv/ pretreated),
- comorbidities and concomitant medication
- life expectancy
- patients from risk categories (homeless population, intravenous drug users, sex industry etc)

*conform to the last Treatment guide from the (NHIH) National Health Insurance House (2015- 2016)

New treatment guides are expected in the next few months.

Clinical an virusological criteria for specific* treatment initiation:

Protocol Interferon + Ribavirin:

- **Biochemistry:** normal/ elevated ALT;
- **Virusological:** serum detected ARN-VHC
- **Histological:** hepatic biopsy, Fibromax cu: A ≥1, F ≥1 and/ or S≥1, Fibroscan F> 1
- **Age**:

  - ≤65 years old.

  - >65 years old (evaluation of treatment opportunity and comorbities)

Anterior treatment status: naive/ pretreated with relapse (NO: non-responders/ virusological breakthrough)

Protocol Interferon- free, direct antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

- **Biochemistry:** normal/ elevated ALT
- **Virusological:** serum detected ARN-VHC , **genotip 1**
- **Histological:** Fibromax **F4 hepatic fibrosis** (compensated hepatic cyrosis -Child-Pugh A)

! F3 conditional of Interferon contraindication (depresive syndrome, psichosis, autoimune syndromes with concomitant treatment, irretrivable diabetes mellitus)

- **Age**: adulti, **indiferent** de varsta
- **Anterior treatment status:** naive/ pretreated

*conform to the last Treatment guide from the (NHIH) National Health Insurance House (2015- 2016)
New treatment guides are expected in the next few months.

Clinical an virusological criteria for specific treatment initiation:

- **Protocol Interferon + Ribavirin:**

Oportunity of the treatment will be evaluated versus comorbities associated risks. The following categories are excluded for interferon therapy option:

- Neurological diseases
- Psichiatric disorders (depressive syndrome, dementia, etc.)
- irretrivable diabetes mellitus
- Autoimmune disorders
- Ischemic coronary disease or irretrivable, severe cardiac failure
- Severe respiratory diseases
- Hb < 11g/dl
- WBC < 5.000 /mm3
- Neutrophiles < 1.500 /mm3

! **haemofilia, talasemia, chronic renal insufficiency + dialysis** may be treated with Interferon + Ribavirine, but need adequate monitoring of the major comorbidity.

- **Protocol Interferon- free, direct antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):**

Contraindication:

- Decompensated cirrohosis,
- Hepatic nodular displazia,
- Chronic alcohol abuse,

! Patients with chronic treatment which is subject to contraindication drug combination listed for Viekirax/ Exviera, will be reevaluated and concomitant medication changed (example: amiodarone, colchicine, ergotamine, simvastatine, midazolam, fusidic acid, carbamazepine, ketoconazol, claritromicine etc)

Treatment schedule:

Protocol Interferon + Ribavirin:

Subcutaneous injection x1/ week: PEGylated Interferon α2a 180μg or PEGylated Interferon α2b 1,5μg/kgc/

plus

Per os: Ribavirine 1000mg/1200mg daily, based on body weight (75 kg).

Recommended duration:

- 24 weeks for 2- 3 genotype (+ ribavirine 800mg/zi),
- 24, 48 or 72 weeks for 1- 4 genotype, based on **baseline HCV RNA:**

- Baseline HCV- RNA < 600.000 UI/ml and RVR (HCV- RNA not detected at week 4) →24 weeks.
- Baseline HCV- RNA > 600.000 UI/ml and HCV- RNA not detected at week 12 → treatment will be continued 48 weeks.

Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Per os: Ombitasvirum+ Paritaprevirum+ Ritonavirum (Viekirax): 2 cp daily in the morning

plus

Dasabuvirum (Exviera): 1 cp daily in the morning and 1 cp daily in the evening

Recomanded duration:

12 weeks.

Monitoring antiviral efficiency

Protocol Interferon + Ribavirin:

HCV- RNA ≥2log lower than baseline or not detected HCV- RNA at:

- 4 weeks
- 12 weeks (in cases with HCV RNA detected at 4 weeks),
- 24 weeks (if not detected HCV RNA never obtainde, but ≥ 2 log lower than baseline at week 12),
- 48 weeks
- 24 weeks after end of treatment- sustained virological response (SVR).

Retreatment PEGylated interferon + Ribavirine in case of relapsed patients:

conform to SPCs, other 48 weeks of treatment with the same criteria as above.

! If detectable ARN-VHC at week 12 of treatment, but lower than ≥2log from baseline → treatment will be continued 24 weeks:

→ still detectable ARN-VHC = stop treatment

→ Not detected ARN-VHC = **treatment to be continued till week 72.**

Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

HCV RNA monitoring, the same as in PEGylated Interferon protocol.

Antiviral efficiency evaluation criteria:

- sustained virological response : not detected HCV RNA at the end of treatment and 12 weeks after end of treatment.
- Therapeutic failure: detected VHC RNA at the end of treatment,
- Relapse: not detected HCV RNA at the end of treatment and detected HCV RNA 12 weeks after end of treatment.

Adverse events monitoring

Protocol Interferon + Ribavirin:

Psichiatrical adverse events: depressive syndrome associated with Interferon

Other adverse events:

- astenia,
- hematological- anemia, trombopenia, leucopenia cu neutropenia,
- loss of appetite,
- weight loss,
- hair loss,
- dermatological disorders (transitional),

may lead to treatment stop based on their severity.

Clinical monitoring will be based on permanent dialog with the patient for efficient action in case of life threatening adverse effects.

! Depression scoring at treatment initiation and collaboration with the psychiatrist.

! Patient's rigorous information about possible adverse events previous treatment start

Protocol Interferon- free, antivirale directe orale (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Psychiatric pre-evaluation/ monitoring: not necessary.

Short duration of the treatment is in favor of getting to lower levels of the adverse event.

Adverse events monitoring

Protocol Interferon + Ribavirin:

Hematological disordes:

- **Anemia-** caused by ribavirin, is treated with Eritropoetine (Epoetinum alfa/ beta) if Hb< 10 g / dl (or >2 g lower in course of 1 week)
- **Neutropenia** – Interferon doses lowering, if < 500 neutrofile/mmc treatment with stimulator of neutrophils colonies (Filgrastim);
- **Trombopenia <** 50.000/mmc -> necesitatea reducerii dozelor de interferon, sau chiar stoparea tratamentului.

! Hematological evaluation is importantant also outside scheduled intervals.

Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Eligible patients for this treatment option in Romania are compensated cirrhotic patients, that is why clinical monitoring is especially based on the clinical and biological signs of cirrhosis decompensation:

- portal encephalopathy
- Ascites decompensation,

In case of appearance of this signs→ stop treatment.

Adverse events monitoring

Protocol Interferon + Ribavirin:

Dermatological adverse events

-cutaneous –dermatitis

-photosensitivity- especially in spring and summer

Usually mild- moderate but can lead to treatment interruption/ stop and need specialist dermatologist monitoring.

Astenia

Digestive disorder and appetite disorder

Weight loss

Hair loss

Teratogenity of the medication needs to be very clear explained to patients before beginning of the treatment- pregnancy must be avoided while on treatment and 6 months

Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Clinical adverse events **(most frequent)**:

- Transitional moderate jaundice,
- Digestive disorders
- Acute renal failure spontaneously resolved or necessiting acute hemodialysis,
- Sudden death.

All patients need to be monitored for adverse events at least 6 months after the SVR, taking into consideration the short period form approval for human use of these drugs.

Drug interactiones

Protocol Interferon + Ribavirin:

- **teofiline** will be cautiously used (P450 1A2 inhibitor); serum levels monitoring especially after first 4 Pegasys doses, daily dose lowering.
- In patients co-infected with hepatitis B virus Peg-Interferon will not be associated with **telbivudine –** because of high risk of periphery neuropatia.
- Ribavirina will not be associated with **azatioprine:** high risk of mielotoxicity
- Biodisponibility of Ribavirine is lowered by co-administration of **antiacides as aluminiu salts and simeticona.**

In patients co-infected with HIV, there are forbidden associations with several anti-retrovirals (see presentation about coinfected patients)

Protocol Interferon- free, oral direct antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

- Contraindication of association of contraceptives sau **etinilestradiol implants.**
- Contraindication of association with **CYP3A4** (substrat) metabolization- dependent drugs because their serum levels will be much higher than expected, causing specific adverse events(conform to SPC section 4.5)
- Medication with high inhibitory effect on **CYP3A4** will not be coadministrated because paritaprevir high levels will be determined (conform to SPC section 4.5)

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Example of very common drug with metabolization strictly dependent on CYP3A4 (substrat) → plasmatic levels much higher than expected→ specific adverse events

- alfuzosin hidrochlorid
- amiodarone
- astemizol, terfenadine
- cisapride
- colchicine (carefully in patients with chronic renal failure)
- ergotamine, dihidroergotamine, ergonovine, metilergometrine
- fusidic acid
- lovastatine, simvastatine, atorvastatine
- midazolam, triazolam (forma per os)
- pimozide
- quetiapine
- quinidine
- salmeterol
- sildenafil (carefully in patients with pulmonary arterial hypertension)
- ticagrelor

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Drugs with moderate/ high enzymatic inductor effect will not be coadministrated →lower plasmatic levels of Viekirax + Eviera, suboptimal for therapeutic effect

- carbamazepine, fenitoine, fenobarbital
- efavirenz, nevirapine, etravirine
- enzalutamide
- mitotan
- rifampicine
- St. John's plant (*Hypericum perforatum*)

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

Medication with high inhibitory effect on CYP3A4 will not be coadministrated because paritaprevir high levels will be determined

- cobicistat
- indinavir, lopinavir/ritonavir, saquinavir, tipranavir,
- itraconazol, ketoconazol, posaconazol, voriconazol
- claritromicina, telitromicina
- conivaptan

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

- Viekirax + chronic **corticoterapy cronica** is not recommended (glucocorticoides metabolized by CYP450, ex: fluticazone) → Ritonavir interaction → higher corticoids exposure → **sindrom Cushing**
- **Lowering colchicine dose** is recommended while on treatment, +/- **interruption (chronic renal failure patients)**
- **- Statines** (Simvastatin, Atorvastatin, Lovastatin, Pitavastatin, Fluvastatin) will not be used while on treatment; <u>exception:</u> **Rosuvastatin** max 5 mg/ day).

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

- Coadministration of all drugs metabolized by **CYP3A (besides drugs presented as contraindication)** must be carefully monitored because higher plasmatic levels are expected for them in combination with Ritonavirum (due to its high inhibitory effect on CYP3A)

For ex: Ciclosporine, tacrolimus (Protopic), amlodipine (Norvasc), rilpivirine, alprazolam, trazodone (Trittico), calcium channels blocants (Nifedipin)

- precaution in coadministration of drugs metabolized by **UGT1A1 glucuronidase** (ex: raltegravir, buprenorfine) → lowering doses will be needed and plasmatic levels monitoring (Viekirax is inhibitor of UGTA1) especially in drugs with narrow therapeutic index (**ex:** Levotiroxine)
- precaution in coadministration of **CYP2C19 substrates → lowering doses will be needed** (**Ex:** lansoprazole, esomeprazole, s-mephenytoin)

Drug interactiones - cont.
Protocol Interferon- free, direct oral antivirals (Ombitasvirum+ Paritaprevirum+ Ritonavirum plus Dasabuvirum):

- **substrates of hepatocellular membranes transporters** OATP1B1, OATP1B3, OATP2B1 or OCT1 need to be administrated in lower doses and plasmatic levels must be monitored

Ex: fexofenadine, repaglinidine, angiotensine II receptors antegonists (Valsartan)

- **substrates of BRCP** (Breast Cancer Receptor Protein) need to be administrated in lower doses and plasmatic levels must be monitored

Ex: sulfasalazine, imatinib, statines

- Precaution at coadministration need also drugs transported by **intestinal P- glycoprotein**.

Ex: dabigatran etexilate (Pradaxa)

Particular aspects of the patients from the disadvantaged/ risk categories, with chronic viral C infection, in Romania

Limitations:

Patients form risk categories (homeless, chronic drugs users, sexual workers) **need higher atention/ implication** from medical staff in order to:

- **be Diagnosed** (low adressibility, lack of continuity)
- **treatment availability** (lack of identity documents, domicile address, National Health Insurance identity, primary care assistance)
- **adverse events monitoring** (high unforeseeable population)
- **compliance conciliation** (usually population with impaired discernment)
- **adverse events and interactions avoidance** by exposure to narcotics and illegal drugs while being treated for VHC- because almost all patients from this categories are chronic “cocktail drug” users.

Particular aspects of the patients from the disadvantaged/ risk categories, with chronic viral C infection, in Romania

Limitations (cont):

The liver is the organ responsible for metabolic biotransformation of substances, but in case of chronic HCV infection it is also the affected organ.

Drug association for different diseases is major practice medical issue. The treatment for chronic hepatitis C is actually an association formula of drugs**:**

- direct antivirals (DAA: direct acting antiviral) with Interferon (classic)
- 3- 4 DAAs (Interferon-free treatment),

ANY other supplementary exogenous substance will be added to this formula of 2, respective 4 or 5 or more if HIV co-infected, all these substances get together into the liver, with specific farmaco -cinetic/ -dinamic/ -toxicological properties.

Because of all these problems this category of patients spontaneously cure for VHC more often than getting to be treated. National health programmes dedicated for this category are missing in Romania that is why they represent increasing epidemiological source.

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Thank you!