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Relevance of the topic

170 mln of patients suffer CVCH worldwide
350 mln suffer CVBH
1 mln of patients dye because of HCC, and hepatic cirrhosis complications.

Alcohol and drugs play role in cancerogenesis

• The results showed more patients with HCC had been frequently overweight (54% compared to 14% of non-HCC patients) or diabetic (43% compared to 22% of non-HCC patients). Half (50%) of patients who had fatty liver disease and were overweight, obese or had type 2 diabetes were found to have HCC compared to just 6% of patients with HCC without these other other conditions.

• Dr. Prati commented: “...patients suffering from alcoholic cirrhosis who also have a history of fatty liver disease, obesity or type 2 diabetes have a higher risk of developing liver cancer. The results will be useful to improve the management of patients with cirrhosis, and to identify cancer at early stages.”
Model for End-Stage Liver Disease (MELD): survival level

- Association between MELD score and 3-month mortality in patients with chronic liver disease

<table>
<thead>
<tr>
<th>MELD score</th>
<th>3-month mortality (%)*</th>
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</thead>
<tbody>
<tr>
<td>≥ 40</td>
<td>100</td>
</tr>
<tr>
<td>30–39</td>
<td>83</td>
</tr>
<tr>
<td>20–29</td>
<td>76</td>
</tr>
<tr>
<td>10–19</td>
<td>27</td>
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<tr>
<td>&lt; 10</td>
<td>4</td>
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</tbody>
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*In hospitalized cirrhotics

HCV-related cirrhosis: a condition with a wide heterogeneity of clinical features

**Compensated (very early stage)**

Often incidentally, diagnosis by histology (F4 Metavir, F5-6 Ishak) or LSM 12.5 kP, no clinical PH, HVPG 6-10 mm, no varicis, Child A5, MELD 10

**Compensated (more severe stage)**

Clinical PH, HVPG 10/12 mm, varicis, PLT 100000, albumin, Child A6-B7

** Decompensated**

Child B7 and more, MELD 15, list of waiting LTx.

Castera L. Gastroenterology 2012

Cirrhosis-related mortality

• Mortality and morbidity, associated with CBH, are caused mainly by cirrhosis and cirrhosis complications
• 5-year cumulative probability of survival
  – Compensated cirrhosis 80–86%
  – Decompensated cirrhosis 14–35%
• Long-term antiviral therapy under close monitoring is proposed according to clinical recommendations for patients with decompensated cirrhosis

Clinical Practice Guidelines

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world’s population has serological evidence of past or present infection with HBV and 350-400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis (CCHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2-4]. HBV-related end stage liver disease or HCC are responsible for over 0.5-1 million deaths per year and currently represent 5-10% of cases of liver transplantation [5-8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) or other co-infections (including alcohol abuse and obesity), can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2-8]. CCHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Mortality and morbidity in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 3-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2-4,11-13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14-35% probability of survival at 5 years [2,4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV, and/or HBV infections; presently it constitutes the fifth most common cancer, representing around 3% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [11]. However, the prevalence of HBV-related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

(1) The “immune tolerant” phase is characterized by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of morphological, mild or no liver abnormalities and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viraemia, these patients are highly contagious.

(2) The “immune active” phase is characterized by HBeAg negativity, relatively lower levels of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or...
Natural history of HBV infection: current view

- **HBeAg**
- **Anti-HBe**
- **HBV DNA**
- **ALT**

**Immune tolerance**
- Immune reactive HBeAg "+" phase
- Inactive carrier state
- HBeAg "-" CBH
- HBsAg "-"
Inactive carriage

Inactive carriage— it is not only normal transaminases level:

DNA less than 2000 IU/ml
HBsAg amount less than 1000 IU/ml

Fibrosis stage monitoring (non-invasive), DNA, ALT.
Viral load significance

HBV DNA more than 2000 IU/ml increases 10-year risk of cirrhosis, HCC and death.

Suppression of viral replication – is a preventative measure for these severe conditions.

Chen C.J Gastroenterol Hepatol 2011,26:628-38.
### Comparison of main guidelines

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<tr>
<td><strong>HBV DNA threshold - HBeAg(+) (UI/ml)</strong></td>
<td>2,000</td>
<td>20,000</td>
<td>20,000</td>
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<tr>
<td><strong>- HBeAg(-) (UI/ml)</strong></td>
<td>2,000</td>
<td>2,000–20,000</td>
<td>2,000</td>
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<tr>
<td><strong>ALT</strong></td>
<td>&gt;ULN</td>
<td>&gt;2x ULN *</td>
<td>&gt;2x ULN</td>
</tr>
<tr>
<td><strong>Factors necessitating therapy beginning</strong></td>
<td>HBV DNA, ALT and liver biopsy (A2 and/or F2), Norm. ALT is allowed</td>
<td>ALT</td>
<td>HBV DNA and ALT</td>
</tr>
<tr>
<td><strong>Biopsy or noninvasive methods of evaluation.</strong></td>
<td>Biopsy in majority of patients, except cirrhosis and in presence of other indications irrespective of biopsy results</td>
<td>In some categories of patient</td>
<td>In some categories of patient</td>
</tr>
</tbody>
</table>

*ULN = 19 U/L in female and 30 U/L in male
Special groups of patients required antiviral therapy

Irrespective of HBV DNA and ALT levels

- Patients with rapid liver function deterioration
- Patients with compensated liver cirrhosis
- Patients with decompensated LC, NA – entecavir, tenofovir (IFN is contraindicated)
- Recurrent HBV-infection after liver transplantation
- HBV carriers, receiving immune suppression therapy or cytotoxic chemotherapy
- Severe course of acute B hepatitis
“...the main goals of HBV treatment is the normalization of ALT activity, persistent inhibition or at least significant suppression of HBV replication and prevent of liver decompensation, HCC and death”

“This goal can be achieved by sustained suppression of HBV replication”

“long-term antiviral therapy is associated with improved liver histology and even reversal of cirrhosis in chronic HBV infection...”

Craxi A. 7th Paris Hepatitis Conference 13-14 January 2014
Among NA monotherapy with tenofovir or entecavir is preferable, because of their high efficacy and minimal risk or resistance (A1). Lamivudin is not recommended.

Close control of HBV DNA performed every 3 months at least during the first year of therapy and until undetectable levels is of great importance, as hepatitis B exacerbation in patients with liver cirrhosis require urgent treatment intervention. These patients require long-term treatment with close control for resistance and exacerbations.

Usually NA therapy in liver cirrhosis patients is extremely long-term. Treatment can be stopped after at least 12 months of consolidating therapy in HBeAg-positive patient, provided confirmed anti -HBe seroconversion or, ideally, loss of HBsAg and anti-HBs seroconversion in HBeAg-negative patients, If they have reached HBsAg loss and anti -HBs seroconversion (B1).
Treatment endpoints

• “Chronic HBV infection cannot be completely eradicated (due to the persistence of ccc-DNA in hepatocytes).
• The ideal end-point is sustained off-therapy HBsAg loss (A1)-rarely.
• A more realistic end-point is a sustained virological remission (absence of DNA) (A1).
• For HBeAg+ patients – HBe seroconversion.
• A maintained virological remission under long-term antiviral therapy in HBeAg-positive patients who do not achieve anti-HBe seroconversion and in HBeAg-negative patients (A1)…»*

*Guidelines 2012
CHB treatment strategies

- IFN (short and pegylated) – time-limited
- NA ограниченная по времени (HBeAg+ with seroconversion)
- NA long-term treatment (HBeAg+ without seroconversion or HBeAg-).

NsA (lamivudine, telbivudine, entecavir, emtricitabine) and NtA (adefovir, tenofovir).

Emtricitabine and PEG- IFN-2b are not licensed in Europe for CHB treatment.
IFN treatment—first-line therapy

- Young woman, planned pregnancy.
- Indicated for time-limited therapy.
- Alt elevated.
- Genotype A
- Low viral load (moderate antiviral effect)
- SVR (2000 IU, N ALT).—in ¼ of patients with HBeAg (-)
- No resistance.
- Unable to use in decompensated cirrhosis,
- List of contraindications.
- Side effects!
- Only for injection formulations.
- Cost.

Could be used in compensated cirrhosis.

Buster E., Hansen B. Hepatology, 2007
Nucleosides (tides) analogues

NA could be used in any genotype, any activity, but are more effective in HBeAg-
High antiviral activity.
Good tolerance, convenient dosing.
In the presence of contraindications to IFN, when IFN is not effective.
Long-term treatment is allowed in decompensated cirrhosis.
Undetermined duration of threatment.
Risk of resistance.
Entecavir, tenofovir – NA with high genetic barrier to resistance.*

*Clinical Practice Guidelines EASL for HBV-infection 2012
The virological efficacy of 1 year of TDV, ETV in patients with HBV decompensative liver disease (Double-blind randomized study)

Respond rates (HBV DNA 400 cop):
TDV (n=45) 71%
ETV (n=22) 73%

ALT-normalization:
TDV (n=45) 57%
ETV (n=22) 55%

HBeAg-seroconversion

IFN -HBe seroconversion after 1 year of treatment is more than 30% and is sustained in 70-87%


AN –22% after 1 year, sustained in 78%. More than 90% after 3 years of treatment with ETV.

HBsAg -seroconversion

**IFN** – 3-5% after 12 months of treatment (EASL 2012),

**After 5 years**– up to 12%.


is lower in high replication and normal ALT.

**AN** – 2% ETV, 1% LMV after 12 m of treatment.

**After 2 years of entecavir treatment** HBsAg loss is 5%. (Gish R, 2007).

Heathcote E., Marcellin P. Gastroenterol 2011,140:132-43
Is the advanced stage of liver damage is reversible?

• Cirrhosis traditionally is regarded as “irreversible fibrosis”
• Regression was described in patients with CBH, receiving antiviral therapy
  – Long-term treatment with ETV and TDF demonstrated histological improvement and cirrhosis reversibility
  – 6-year therapy with ETV improved fibrosis scores according to Ishak scale in 88% of patients with advanced stage of the disease and cirrhosis.
• Reversibility - important concept to consider as a goal of treatment

Is the advanced stage of liver damage is reversible?

- 5 –years treatment with ETV or TDV in patents with compensated cirrhosis decreased the risk of clinical decompensation (ascites, HE, icterus, hemorrhage)
- AVT increased survival in patients with decompensated cirrhosis, as suppression of HBV replication leads to reversal of decompensation in many patients.

Decrease of Child-Pugh score by ≥2 (clinical and laboratory improvement)

Improvement of liver function was also confirmed by decrease of MELD index during antiviral therapy

Liaw YF. et al., Hepatology. 2011 Jul;54(1):91-100
VIRGIL Study (n=372)

Компенсированный цирроз – 89
Декомпенсированный цирроз – 9
Без цирроза – 274

20 мес. ETV

Вирусологический ответ ассоциировал с более низким риском ГЦК и смерти.

Patients with severe fibrosis and cirrhosis. Treatment ETV.

Fibrosis (Ishak)

- 6
- 5
- 4
- 3
- 2
- 1
- 0

patients (n)

0 48 ws ~6 yrs

n=10

BMS Data On File: Study 901 long-term histology report Sept 2008
Long-term treatment with entecavir caused fibrosis reversion in patient with HBV-associated hepatic cirrhosis.

Masson Trichrom staining: blue staining - fibrose tissue

Baseline
Fibrosis according to Ishak scale = 6

Week 48
Fibrosis according to Ishak scale = 6

After 1 year of therapy - No regression

After 5 years of therapy – cirrhosis regression

Week 268
Fibrosis according to Ishak scale = 2

According to Ishak scale = 6

According to Ishak scale = 2
Rate of development of resistance to nucleos(t)ides analogues in CBH

When to stop treatment?

In HBeAg(+) patients the goal of treatment – sustained HBeAg seroconversion with HBV DNA level of <2000 IU/ml, normal ALT level or even HBsAg seroconversion.

Treatment should be stopped after 12 months, after HBeAg seroconversion.

• HBeAg(-)  Sustained HBsAg elimination with or without seroconversion, viraemia suppression on treatment can predict sustained response achievement in off-treatment setting

New surrogate markers, such as cccDNA and quantitative measurement of HBsAg could be of more prognostic value to predict off-treatment response maintenance.
Nucleosides analogues

ETV, TDV – effective HBeAg treatment, good tolerance, effective replication suppression without resistance, with high level of biochemical remission, histological improvement and prevention of clinical decompensation, possibly, HCC.

Indicated for decompensated patients, “severe liver disease”, with contraindications to IFN, when IFN is not effective.
Successful therapy of HCV liver cirrhosis (SVR) is associated with decreased incidence of HCC, decompensation and liver-related mortality (Morgan 2010 van der Meer 2012).

IFN-based treatment should be limited to cirrhotic patients.

IFN-free DAA combinations are the best option?

Treatment of HCV-associated cirrhosis

PI (BOC, TVR) optimized the efficacy of antiviral therapy

REALIZE: fibrosis stage is important factor for TVR efficacy

SVR 58% Metavir F3-4 75% F0-2
Null-R SVR 14% F3-4 41% F0-2

Decompensated patients are not included

Bruno S., Mangia A, Dig Liver Dis 2013, 45:356-61
Safety worsens in advanced liver disease
Treatment of HCV-associated cirrhosis

SPRINT-2 RESPOND-2 PROVIDE (meta-analysis)
Patients with significant fibrosis and cirrhosis. F4
BOC/PR SVR - 55%.
Bruno S., Vierling JM, J. Hep 2013, 58:479-87

CUPIC BOC, TPV (HCV compensated cirrhosis,
non-responders, genotype 1, n=292)
At Week 12 RNA (-) 78%, SVR12 - 40%
Death, decompensation, serious infections - 6.4%
Hezode C, Fontaine H, J. Hep 2013, 59:434-41
### Table: CUPIC: SVR12 and the risk of occurrence of severe complications

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Complications, n (%)</th>
<th>SVR12, n (%)</th>
<th>Platelets count ≤100,000/mm³</th>
<th>Platelets count &gt;100,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 g/L</td>
<td>N</td>
<td>37</td>
<td>31</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td></td>
<td>Complications</td>
<td>19 (51.4)</td>
<td></td>
<td>9 (29.0)</td>
</tr>
<tr>
<td></td>
<td>SVR12</td>
<td>10 (27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35 g/L</td>
<td>N</td>
<td>74</td>
<td>306</td>
<td>19 (6.2)</td>
</tr>
<tr>
<td></td>
<td>Complications</td>
<td>9 (12.2)</td>
<td></td>
<td>168 (54.9)</td>
</tr>
<tr>
<td></td>
<td>SVR12</td>
<td>27 (36.5)</td>
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</table>

*Missing data for 63 patients

Severe complications include death, hospitalisation and hepatic decompensation.
Treatment of HCV-associated cirrhosis

SOF+PR 12ws

NEUTRINO 327 naïve, G 1, 4, 5, 6 (17% cirrhosis)

SVR12 G1-89%, G4-96%, G5, 6-100%.

Cirrhosis-80%.

NEUTRINO: SVR12 by Sofosbuvir + P/R (12 weeks) According to Genotype and Fibrosis Level

**SVR12 According to Genotype**

- GT 1: 89% (261/292)
- GT 4: 96% (27/28)
- GT 5,6: 100% (7/7)

**SVR12 According to Fibrosis Level**

- No Cirrhosis: 92% (252/273)
- Cirrhosis: 80% (43/54)

*Lawitz E, et al. NEJM 2013*
Treatment of HCV-associated cirrhosis

SOF+ R 12ws and PR 24ws

FISSION (n=499 G2,3 cirrhosis 20-21%)
SVR12 cirrhosis G2 91% SOF/R, 61% PR
   G3 34% 30%

FUSION (33-35% cirrhosis comp.)
SOF + R 12,16 ws
SVR12 G2 78%(16ws), 60%(12ws)
   G3 61%(16ws), 19%(12ws)

Treatment of HCV-associated cirrhosis

SMV+PR
ASPIRE G1 F3-4
SVR24 65%(relapser), 67%(partial response), 31%(null-r)

SMV+PR, PR
QUEST-1 cirrhoses SVR12 58%SMV, 29%PR
QUEST-2 SVR12 65%SMV, 40%PR

Manns M, Marcellin P, EASL 2013, abstr 1413
Simeprevir plus PegIFN and Ribavirin in treatment-experienced patients with HCV Genotype-1 infection (the ASPIRE trial)

SVR 24 (%)

<table>
<thead>
<tr>
<th>Relapsers</th>
<th>Partial responders</th>
<th>Null responders</th>
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<tbody>
<tr>
<td>FO-F2 F3 F4</td>
<td>FO-F2 F3 F4</td>
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<tr>
<td>56</td>
<td>92</td>
<td>95</td>
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<td>0</td>
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*duration groups pooled


S.Bruno PHC 2014
Treatment of HCV-associated cirrhosis

COSMOS    SMV+SOF+-/R 12ws
Patients with and without cirrhosis, naïve and non-responders.
SVR4 96%
SVR4 100% (+R)

Lawitz E., Ghalib R. 20th Conf on Retrovirusis and Opport Inf 2013, abstr 155LB.
Treatment of viral cirrhoses

- Pathogenetic treatment
- Treatment of complications
HE treatment: integrated approach

• Diet
• Lactulose
• Rifaximin
• Pro- & prebiotics
• L-Ornithine-L-Aspartate (LOLA)
Increase of ammonia detoxification in liver and tissues

L-ornithine-L-aspartate (Hepa-Merz): coenzyme and substrate for urea and glutamine synthesis

Starting from 1970-ies is used in treatment of HE.

L-Ornithine-L-Aspartate – hepatoprotector- detoxicant. Hepatoprotective properties today are proved.

Grungraiff K., 2004 (1167 pts.) Chen M.F., Li R.C. et al, 2005
Burkov S.G., Arutyunov A.G., 2010, Osipenko M.F. et al., 2010
L-Ornithine-L-Aspartate: Mode of Action

- detoxication, ammonium binding
- Improvement of portohepatic haemodynamics
- Improvement of hepatocytes regeneration
- Stimulation of energy processes, of redox processes in hepatocytes
- Anabolic effect (increase if protein synthesis
- Improvement of hepatocyte function

Detoxification

**L-Ornithine-L-Aspartate** - natural part of metabolic chain, 80% of the main endotoxin – ammonia is detoxified in ornithine cycle.

- Direct influence on ammonia neutralization – activation of urea synthesis in liver, glutamine synthesis in liver and muscles
- Ornithine and aspartate – are the substrates for this synthesis
- Aspartate integrates in ornithine cycle, lactic acid synthesis is decreased, BBB permeability for toxic substances is decreased

Double detoxification effect compared to other drugs action – direct detoxification and indirect action via improvement of hepatocytes function.

Ларионова В.Б., Рябухина Ю.Е. Возможности лечения и профилактики печеночной токсичности у онкологических больных //Сопроводительная терапия в онкологии, 2006. - №2.
L-Ornithine-L-Aspartate: Mode of Action

Improvement of portohepatic haemodynamics

**Polyhepatography** – modified hepatic impedancemetry to assess portohepatic haemodynamics, intrahepatic circulation. PHG allows to measure blood perfusion in right and left hepatic lobes, spleen, to perform impedance plethysmography (4 leads totally), ECG and PCG.

PHG also includes vasodilation test using nitrates and deep breath. Sensitivity to determine the level of hemodynamic blockage is 92%, specificity is 93%, in determining of PH – 92% and 93%.

Measurement of hemodynamics during L-ornithine-L-aspartate usage

1- REO before Hepa-Merz dosing
2- REO after Hepa-Merz dosing

Ермолов С.Ю. Ермолова Т.В., патент №2286773
Improvement of portohepatic haemodynamics

L-ornithine-L–aspartate improved intrahepatic circulation parameters in patients with different types of portohepatic haemodynamic disturbances

• Improvement of portohepatic haemodynamic disturbances and portal hypertension is an important factor for optimizing the pathogenetic therapy in CLD.
• Improvement of portohepatic circulation promotes regeneration and restoration of hepatocytes function, prevents liver fibrosis progression.
• *Hepa-Merz– is vasoactive medicinal product, via arginine synthesis it increases NO synthesis*

**L-Ornithine-L-Aspartate: Mode of Action**

**Hepa-Merz**— *is vasoactive drug*, via arginine synthesis stimulation it increases NO synthesis, improving circulation in different organs (liver, muscles, brain, pancreas).

Ермолова Т.В., Ермолов С.Ю., Добкес А.Л., 2009.
Ткач С.М., 2013.
L-Ornithine-L-Aspartate: Mode of Action

Anabolic effect

• Ornithine increased insulin production, STH.
• Ornithine increased proteine synthesis, increases spermine, glutamate, and prolne synthesis, increases RNA, DNA, and protein biosynthesis in liver and muscles
• Ornithine increased lipid catabolism

This mechanism of action optimized use of the medicinal product in CLD, cirrhoses, oncology, sports medicine.

Никонов В.В., Нудьга А.Н.,2011
L-Ornithine-L-Aspartate: Mode of Action

Improvement of regeneration?

- Concurrently with portohepatic hemodynamic disturbances correction.
- Concurrently with increase of protein synthesis
- By means of improvement of energy processes in damaged cells (hepatocytes), active transport of aspartate through cell membranes, involvement in Krebs cycle, tricarbonic acid cycle in mitochondria, improvement of energy processes in damaged cells (hepatocytes), stimulation of energy processes via increased lipid catabolism.
L-Ornithine-L-Aspartate: Mode of Action

Membrane-stabilizing component in LOLA pharmacodynamics?

Medicinal product promotes restoration of erythrocytes biomembranes lipid spectrum – decrease of membrane-destructive processes in the body.

Кукес В.Г., Крылов В.Г. И др.
Клиническая фармакология и терапия.2010.-№1.
L-Ornithine-L-Aspartate: Mode of Action

Hepa-Merz is a hepatoprotector and detoxicant with pleiotropic effect

Is effective in prevention and treatment of hepatic insufficiency in liver cirrhosis and acute hepatitis, and also in treatment of chronic hepatitis of different aethiology

Шульпекова Ю.О., Федосьина Е.А., Маевская М.В., Ивашихин В.Т., 2005.
Chen M.F., Li RC et al, 2005 Ткач С.М., 2013
Волчкова Е.В. и соавт.2010 Спиридонова Э.А.2004
Ермолова Т.В. и соавт. Современная гастроэнтерология и гепатология, №1, 2012.
Course at prevention of HE

- Early diagnosis of chronic viral hepatitis, early staging
- **Etiotropic therapy in patients with chronic hepatitis, in cirrhosis stage**
- Determination of trigger factors for the prevention provoked HE
- Long term use of L-ornithine-L-aspartate, lactulose, rifaximin in persistent HE
HCV-reinfection occurs in 20-30% patients after transplantation and lead to rapid progression to cirrhosis within the first 5 years. Urgent treatment! Retransplantation?

IFN-based treatment (PR- 30% SVR, side effects, drug-drug interaction)

IFN-free therapy (SOF+RBV)-potential all-oral therapy after Tx  Charlton 2013.

Roche, Liver Transpl. 2008
HCV reinfection after LTx

Triple therapy (PI+PR)
SVR24 TPV 27%, BOC 47%.
Cessation of therapy with BOC 48%, TPV 61%.

Coilly AASLD 2013
## Discontinuation and failure

<table>
<thead>
<tr>
<th>Reason</th>
<th>BOCEPREVIR</th>
<th>TELAPREVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature discontinuation (n/%)</td>
<td>17 (48%)</td>
<td>27 (61%)</td>
</tr>
<tr>
<td>Discontinuation for AE (n/%)</td>
<td>7 (20%)</td>
<td>14 (32%)</td>
</tr>
<tr>
<td>Other reasons (n)</td>
<td>1 HCC recurrence</td>
<td>1 reLT</td>
</tr>
<tr>
<td>Treatment failure during treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response (n/%)</td>
<td>5 (14%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Null response (n/%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Virological breakthrough (n/%)</td>
<td>3 (9%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Treatment failure after treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse (n/%)</td>
<td>3 (9%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
HCV reinfection after LTx

Combinations without IFN are preferable (SOF+RBV) 100% after treatment, SVR4 77% Charlton 2013.

Daclatasvir + sofosbuvir

SOF+R+/-Ledipasvir 12,24ws (NCT01687270)
Experience with second generation DAA
Sofosbuvir + ribavirine for HCV recurrence after LT

- Multicentric prospective study: 40 patients (6-150 month post-LT)
  - G1 (83%), fibrosis ≥ F3 (63%), previously treated (88%)
  - No inclusion if decompensated cirrhosis, steroids > 5 mg/d, Child-Pugh > 7, MELD > 17
  - Immunosuppression: tacrolimus (70%), cyclosporine (25%)

Study design
SOF 400 mg + RBV 400-1 200 mg (n = 40) → SVR12

Virological response

* 1 patient is still under treatment
** 4 patients did not reach the W28 visit

Chariton M, AASLD 2013, Abs. LB2
Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection After Liver Transplantation

Michael P. Curry, Xavier Forns, Raymond Chung, Norah Terrault, Robert Brown Jr., Jonathan M. Fenkel, Fredric Gordon, Jacqueline O'Leary, Alexander Kuo, Thomas Schiano, Gregory Everson, Eugene Schiff, Alex Befeler, John G. McHutchison, William T. Symonds, Jill Denning, Lindsay McNair, Sarah Arterburn, Dilip Moonka, Edward Gane, Nezam Afshar

1Beth Israel Deaconess Medical Center, Boston, MA; 2The Liver Unit, Barcelona, Spain; 3Massachusetts General Hospital, Boston, MA; 4University of California, San Francisco, CA; 5Columbia University, New York, NY; 6Thomas Jefferson University Hospital, Philadelphia, PA; 7Lahey Clinic, Burlington, MA; 8Baylor University Medical Center, Dallas, TX; 9University of California, San Diego, La Jolla, CA; 10Mount Sinai School of Medicine, New York, NY; 11University of Colorado, Denver, CO; 12University of Miami, Miami, FL; 13St Louis University, St. Louis, MO; 14Gilead Sciences, Inc., Foster City, CA; 15Henry Ford Health System, Detroit, MI; 16Auckland City Hospital, Auckland, New Zealand

AASLD 2013, Washington, DC
HBV reinfection after LTx

Before LTx – NA in all cases (A1)

After LTx – ETV

(Fung J. Gastroenterology, 2011, 141: 1212-19).

Emtricitabine + tenofovir +/- HBVJg

(Teperman L. Hepatology 2010, 52:S12-13.)
Prophylaxis HBV

In post-LTx period:

long-term prophylaxis with HBV Ig improves the survival rate at the patients HBsAg+.


Antibody level should be at least 100 IU
Thank you for your attention!