HEPATOPROTECTORS PLACE IN THERAPY OF CHRONIC VIRAL HEPATITIS

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Hepatoprotectors and chronic viral hepatitis

• Do patients with chronic viral hepatitis need hepatoprotectors?
• At what times of illness it is advisable the appointment of hepatoprotectors?
• What are the indications for use hepatoprotectors in chronic viral hepatitis?
• It is necessary to appoint hepatoprotectors during antiviral therapy?
Contradictory attitude to hepatoprotectors at CVH

- The heterogeneity in origin and chemical composition
- The lack of a common mechanism of action
- The lack of randomized clinical trials on the efficacy and safety
- The lack of specific indications for use
- Self-acceptance by patients, the lack of supervision by a doctor
Hepatoprotectors - drugs that protect the liver from the damaging effects of exogenous or endogenous factors that reduce inflammatory activity and the rate of disease progression.

The basis of action all hepatoprotectors is impact on pathogenetic mechanisms, but not the cause of liver disease.
Hepatoprotectors

• There are registered for about 30 drugs that claim to the title of "hepatoprotector" in Russia
• They make up about 10% of the total number of drugs in the Russian market
• A number of homeopathic remedies, nutritional supplements and other alternative health products positioned as hepatoprotectors
• The United States each year is spending on nutritional supplements about $6 billion, herbs and teas about $1 billion
• Europe (mainly Germany) each year is spending on silymarin about 150 million €
Classification of hepatoprotectors

• Herbal preparations (silymarin, glycyrrhizin acid and other)
• Amino acids and their derivatives (Ademethionine)
• Bile acids (ursodeoxycholic acid, chenodeoxycholic acid)
• Essential phospholipids
• Vitamins and antioxidants
• Other
Basic mechanisms of action hepatoprotectors (proven and inferred)

- stabilization of cell membranes and organelles
- antioxidant effect
- detoxicant effect
- anti-inflammatory effect
- anti-holestatic effect
- antifibrotic effect
- stimulation of liver regeneration
- antidepressant effect
- immunomodulatory effect
Application hepatoprotectors

• Autoimmune hepatitis
• Primary biliary cirrhosis
• Primary sclerosing cholangitis
• Acute and chronic hepatitis with cholestatic component (especially alcohol and drugs)
• Mucoviscidosis
• Cirrhosis of any etiology
• Atresia of the intrahepatic bile ducts
• Post-transplant cholestasis
• Cholestasis with parenteral nutrition
• Intrahepatic cholestasis of pregnant
• NASH
• Psoriasis, atopic dermatitis, eczema
• Chronic viral hepatitis
The basic principles of treatment of chronic viral hepatitis

1. Complexity

Effects on the pathogen
Interferon-alpha, drugs with direct antiviral effect

Effects on reactivity
Interferon-alpha, cytokines, oxygen therapy, extracorporeal blood correction, etc.

Impact on the pathogenesis
Vitamins, sorbents, polyenzyme drugs, infusion-detoxification and metabolic therapy, 
hepatoprotectors, immunosuppressants, efferent therapy

2. Individuality

3. Timely start
At what times of the current CVH should appoint pathogenetic therapy?

- The lack of indications for antiviral therapy (phase immune control of HBV)
- The remission after antiviral therapy
- The impossibility of antiviral therapy (absolute contraindications)
Indications for use hepatoprotectors in chronic viral hepatitis (pathogenetic therapy)

• Chronic viral hepatitis with the development of cholestasis (ademetionine, UDCA)

• Concomitant metabolic and toxic liver disease (essential phospholipids, glycyrrhizin acid, vegetable hepatoprotectors)

• Associated pancreatic and biliary disease (ademetionine, UDCA, hepatoprotectors with choleretic effect)
42% of patients with CHC have got clinical, laboratory and instrumental signs of pancreatic and biliary disease (n=465)

1 - Dysfunction of the biliary system
2 - GSD, calculous cholecystitis
3 - Chronic pancreatitis

D. Gusev, 2007
The incidence of pancreatic and biliary disease depends on the stage of CHC(%)
Main features of pancreatic and biliary disease in patients with CHC

- The prevalence of dysfunction (hypotension) gall bladder

- Direct correlation between the frequency of pancreatic and biliary disease and duration of hepatitis C in the absence of interaction with the activity of the pathological process in the liver

- Frequent combination of biliary dysfunction with clinical and laboratory signs of chronic pancreatitis and intestinal dysbiosis, especially in patients with F3-4

- The worsening pancreatic and biliary disease on antiviral therapy against HCV (65%)
Indications for use hepatoprotectors on CVH antiviral therapy (supporting therapy)

- The potentiating of the antiviral effect of treatment (ademetonine, glycyrrhizin acid, silymarin)?
- The correction of adverse events of interferon-alpha and ribavirin:
  - Ademetionine (cytolytic crises, cholestasis, depression),
  - Ursodeoxycholic acid (cholestasis, dysfunction of the biliary system),
  - Metadoxil (depression).
Effectiveness of UDCA for chronic hepatitis C (EOT and SVR)

IFN 3 million ME 3/week – 24 weeks
UDCA 15 mg/kg - 24 weeks

K.Zhdanov, D.Gusev, 1998
HCV induces a violation of methylation controls transcription of IFN-α - activated genes indicating inefficient AVT

Duong F.H., 2006
Demethylation processes are due to excess SPAT HCV-induced production of the protein phosphatase catalytic subunit 2A (PF2Ak), which binds and blocks arginimethyltransferase (AMT), which carries out methylation of SPAT.

In an HCV genotype 1 observed more intense than in other genotypes PF2Ak products, which leads to low efficiency of the AVT.

By transmethylation ademetionine (donor of methyl groups) restores the enzyme activity of AMT and increases the number of methylated SPAT and restores transcription of IFN-stimulated genes, in consequence, increases the effectiveness of antiviral therapy.

Duong F.H., 2006
Study the effect of ademetionine on the effectiveness of interferon-α and ribavirin for CHC

Baseline data

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Study group (ademetionine+)</th>
<th>Control group (ademetionine-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=</strong></td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Men / Women</td>
<td>8 / 5</td>
<td>12 / 8</td>
</tr>
<tr>
<td>Mean age</td>
<td>32.7 ± 6.7</td>
<td>30.1 ± 11.3</td>
</tr>
<tr>
<td>Genotype 1 / non-1</td>
<td>10 / 3</td>
<td>13 / 7</td>
</tr>
<tr>
<td><strong>Histological activity (METAVIR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>A2</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>A3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Fibrosis (Desmet V. et al., 1995)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>F2</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>F3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>F4</td>
<td>2</td>
<td>-</td>
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</table>

K.Zhdanov, D.Gusev., 2008
Study the effect of ademetionine on the effectiveness of interferon-α and ribavirin for CHC

K.Zhdanov, D.Gusev., 2008

Baseline data

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<th>Control group (ademetionine-)</th>
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</thead>
<tbody>
<tr>
<td>Bilirubin total, μmol/l</td>
<td>33,3 ± 2,34*</td>
<td>25,2 ± 3,9*</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>151,8 ± 61,7</td>
<td>155,5 ± 58,7</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>85,5 ± 8,8</td>
<td>88,2 ± 10,13</td>
</tr>
<tr>
<td>Alk Phos, U/l</td>
<td>142,2±24,7**</td>
<td>91,2±15,3**</td>
</tr>
<tr>
<td>γ-GTP, U/l</td>
<td>85,8±16,1*</td>
<td>54,1±12,0*</td>
</tr>
</tbody>
</table>

* - p <0,05; ** - p <0,01
Study the effect of ademetionine on the effectiveness of interferon-α and ribavirin for CHC

Results

SVR, %

<table>
<thead>
<tr>
<th>Group</th>
<th>Study (%)</th>
<th>Control (%)</th>
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</thead>
<tbody>
<tr>
<td>G 1</td>
<td>40.0*</td>
<td>15.4*</td>
</tr>
<tr>
<td>G non-1</td>
<td>66.7</td>
<td>57.1</td>
</tr>
</tbody>
</table>

* - p < 0.05

K. Zhdanov, D. Gusev, 2008
Study the effect of ademetionine on the effectiveness of interferon-α and ribavirin for CHC

G 1, SVR -

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>Control</th>
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<tbody>
<tr>
<td>Bilirubin</td>
<td>100*</td>
<td>100**</td>
</tr>
<tr>
<td>ALT</td>
<td>75*</td>
<td>75*</td>
</tr>
<tr>
<td>AST</td>
<td>9*</td>
<td>9*</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>36,7**</td>
<td>36,7**</td>
</tr>
<tr>
<td>GGTP</td>
<td></td>
<td></td>
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</tbody>
</table>

Results

* - p=0.01;  ** - p=0.03

K.Zhdanov, D.Gusev., 2008
Study the effect of ademetionine on the safety of interferon-α and ribavirin for CHC

results

* - p < 0.05

K.Zhdanov, D.Gusev., 2008
Effect of glycyrrhizic acid on the effectiveness of interferon-α and ribavirin for chronic hepatitis C

Abe Y., 2004
PHG-M3/P01-09 «ORION» - Open comparative randomized trial of the Phosphogliv in combination therapy patients with chronic hepatitis C

Group A
Phosphogliv
4 weeks

Group A
Phosphogliv + AVT
4 weeks

Group A
Phosphogliv Forte + AVT
44 weeks for genotype 1
20 weeks for genotype 2 and 3

Group B
AVT
48 weeks for genotype 1
24 weeks for genotype 2 and 3

Visits 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Visits 0, 1, 2, 3, 4, 5, 6, 7, 8

End therapy

SVR

24 weeks

24 weeks

genotype 1 48 weeks

genotype 2 и 3 24 weeks

Preliminary results:
RVR at 1 genotype was observed only in patients receiving triple therapy (17%)
Silibinin in antiviral therapy for chronic hepatitis C
(preliminary results)

Patients with non-response to combination therapy with peg-IFN and ribavirin.

Silibinin 20 mg / kg parenterally in conjunction with standard antiviral therapy - there was a significant reduction in viral load.

P. Ferenci, 2008
Conclusion

• Hepatoprotectors can be used in the complex pathogenetic therapy in patients with chronic viral hepatitis.

• Indications for use hepatoprotectors in patients not receiving antiviral therapy are associated metabolic and toxic liver injury and diseases pancreatic and biliary system.

• Hepatoprotectors can be used to correct some adverse effects of antiviral therapy for chronic viral hepatitis.

• Some hepatoprotectors (primarily ademetionine and silymarin) claim to potentiate the effect of antiviral therapy. This question requires further research.
Hepatoprotectors place in the therapy of chronic viral hepatitis is determined according to the pathogenetic mechanism of action within a clearly differentiated indication for use in patients receiving and not receiving the AVT.