Ciroza Biliară Primitivă

Ghid de diagnostic si de tratament

1. Definitie

Ciroza biliara primitiva (CBP) este o granulomatoza progresiva nonsupurativa autoimuna cu afectarea progesiva a ductelor biliare, ductopenie si sindrom de colestaza intrahepatica.

2. Diagnostic

Criteriii de diagnostic pentru CBP (2 din 3)

- AMA detectabili (> 1:40)
- Fosfataza alcalina crescuta (> 6 luni)
- Histologie sugestiva

3. Tratament

3.1 Introducere

3.1.1 Obiectivele tratamentului:

- reducerea mortalitatii
- cresterea duratei de viata
- prevenirea complicatiilor
- prevenirea transplantului hepatic
- imbunatatirea calitatii vietii

3.1.2 Masuri terapeutice:

- regim igienodietetic
- etiologice
- patogenice
- simptomatice
- a complicatiilor

3.1.2.1 Regimul igieno-dietetic.

Spitalizarea pacientilor este obligatorie in urmatoarele situatii: luarea in evidenta, initierea unor noi clase de medicamente, aparitia unei complicatii, controlul semestrial, la solicitarea pacientului **(III).**

Efortul fizic trebuie redus si rationalizat conform stadiului bolii, complicatiilor, varstei, profesiei, starilor comorbide. Durata minima de repaus la pat este de 8-10 ore **(III).**

Dieta recomandata: hiposodata, hipocolesterolemianta, normo sau hipoproteica, normoglucidica, bogata in vitamine, cu supliment de vitamine liposolubile (vit. A, D, K) si saruri minerale (calciu, magneziu, potasiu) **(III).** Cantitatea de NaCl admisa pe zi nu trebuie sa depaseasca 3-4 g/zi initial, 1-2 g/zi in stadiile Child B si C ale cirozei. Din dieta se reduc sau se exclud grasimile de origine animala **(III).** Cantitatea de proteine admisa pe zi este de 0,5 g/kgc/zi **(III).** Datorita sindromului de malabsorbtie sunt necesare suplimente importante de vitamina A, D si K si de calciu, potasiu si magneziu. Din acest motiv trebuie incurajata dieta bazata pe legume si fructe bogate in aceste vitamine: morcovi, telina, sfecla, spanac, stevie, praz, mere, pere, prune, coacaze, banane **(III).**

3.1.2.2 Tratamentul etiologic.

Nu dispunem de dovezi privind tratamentul etiologic.

3.1.2.3 Tratamentul patogenic.

• **Acidul ursodeoxicolic (AUDC)**
• **Derivatii acidului fibric** - *bezafibrat* - *fenofibrat*

• **Imunosupresive** - *corticosteroizi* - metilprednisolon - budesonide - *azathioprina* - *metotrexat* - *ciclosporina*
• **Colchicina**

Acidul ursodeoxicolic - AUDC (Ursofalk®) este prima optiune terapeutica. Doza recomandata este de 13-15 mg/kgc/zi timp de 4 ani **(I).** Intre momentul administrarii UDCA si al colestiraminei trebuie sa treaca 4 ore pentru a preveni interferente privind absorbtia. Asocierea AUDC cu alte medicamente (colchicina, metotrexat, cortico- steroizi) nu confera avantaje fata de monoterapia cu AUDC **(III).**

Bezafibratul si fenofibratul amelioreaza tabloul biochimic al bolii singuri sau asociati cu AUDC. Nivelul colesterolului si al trigliceridelor scade semnificativ **(IIC).**

Colchicina amelioreaza tabloul histologic si reduce riscul complicatiilor si necesitatea transplantului hepatic **(III).**

*Medicatia imunosupresiva (*azathioprina, metotrexat sau ciclosporina*)* nu a confirmat.

18. Mitchinson HC, Palmer JM, Bassendine MF, Watson AJ, Record CO, James OFW. A controled trial of prednisolone treatment in primary biliary cirrhosis. Three years results. J Hepatol 1992;15:336-344
19. Kaplan MM, Knox TA. Treatment of primary biliary cirrhosis with low-dose methotrexate. Gastroenterology 1991;101:1332-1338
20. Heathcote EJ. Management of primary biliary cirrhosis. Hepatology 2000;31:1005-1013
21. Poupon RE, Ouguerram K, Chretien Y, Vernau C, Eschwege E, Magot T, Poupon R. Cholesterol-lowering effect of ursodeoxycholic acid in patients with primary biliary cirrhosis. Hepatology 1993;17:577-582
22. Datta DV, Sherlock S. Treatment of pruritus of obstructive jaundice with cholestyramine. BMJ 1963: 216-219
23. Javitt NB. Timing of cholestyramine doses in cholestatic liver disease. N. Engl. J Med 1974; 290:1328-1329
24. Ghent CN. Pruritus of cholestasis is related to effects of bile salts on the liver, not the skin. Am J Gastroenterol 1987; 82:117-119
25. Bachs L, Pares, Elena M, Piera C, Rodes J. Effects of long-term rifampicin administration in primary biliary cirrhosis. Gastroentorology 1992; 102: 2077-2080.
26. Berdasa NV, Alling DN, Talbot TL, Swain MG, Yurdaydin C, Turner ML, Schmidt JM. Effects of naloxone infusions in patients with the pruritus of cholestasis: a double-blind, randomized, controlled trial. Ann Intern Med 1995; 123:161-167
27. Wolfhagen FHJ, Sternieri E, Hop WCJ, Vitale G, Bertolotti M, Van Buuren HR. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. Gastroenterology 1997; 113:1264-1269
28. Levy C, Lindor KD. Management of osteoporosis, fat-soluble vitamin deficiencies, and hyperlipidemia in primary biliary cirrhosis. Clin Liver Dis 2003; 7:901-10
29. Guanabes N, Pares A, del Rio L, Roca M, Gomez R, Munoz J, Rodes J. Sodium flouride prevents bone loss in primary biliary cirrhosis. J Hepatol 1992; 15:345-464
30. Menon KV, Angulo P, Boe GM, Lindor KD. Saffety and efficacy of estrogen therapy in preventing bone loss in primary biliary cirrhosis. Am J Gastroenterol 2003; 98:889-92

7. Setchell KDR, Rodrigues CMP, Clerici C, Solinas A, Morelli A, Gertung C, Boyer J. Bile acid concentration in human and rat liver tissue and hepatocyte nuclei. Gastroenterology 1997;112: 226-235
8. Calmus Y, Weill B, Ozier Y, Chereau C, Houssin D, Poupon R. Immunosuppressive proprieties of chenodeoxycholic and ursodeoxycholic acids in mouse. Gastroenterology 1992;103: 617-622
9. Poupon RE, Poupen R, Balkau B. The UDCA-PBC Study Group. Ursodiol for the long-term treatment of primary biliary cirrhosis, N. Engl. J Med 1994; 330:1342-1347
10. Lindor KD, Dickson ER, Baldus WP. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994; 106:1284-1290
11. Combes B, Carithers RS RL, MADDREY WC. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995; 22:759-766
12. Ishibashi H, Shimoda S, Gershwin M E,"The immune response to mitochondrial autoantigens", Semin Liver Dis 2005;25: 337–346.
13. Nakai S, Masaki T, Kurokohchi K. Combination therapy of bezafibrat and ursodeoxycholic acid in primary biliary cirrhosis: a preliminary study. Am J Gastroenterol 2000;95:326-327
14. Kurihara T, Maeda A, Shigemoto M. Investigation into the efficacy of bezafibrate against primary biliary cirrhosis, with histological references from cases receiving long term momotherapy. Am J Gastroenterol 2002;97:212-214
15. Yano K, Kato H, Morita S. Is bezafibrate histollogially effective for primary biliary cirrhosis? Am J Gastroenterol 2002;97:1075-1077.
16. Christensen E, Neuberger , Crowe J, Altman DG, Popper H, Portmann B, Doniach D. Beneficial effect of azathioprine and prediction of prognosis in primary billiary cirrhosis: final results of an international trial. Gastroenterology 1985;89: 1084-1091
17. Lombard M, Portmann B, Neuberger J. Cyclosporin A treatment in primary biliary cirrhosis: results of a long term placebo controlled trial. Gastroenterology 1993;104:519-526

3.1.2.4. Tratamentul simptomatic.

3.1.2.4.1. Pruritul

a) colestiramina 2,5-5 g de 3 ori pe zi, zilnic ca prima optiune **(III)**
b) rifampicina 150 mg de 2-3 ori pe zi, zilnic in cazurile care nu raspund la colestiramina **(III)**
c) antagonisti opioizi (Naloxone) in cazurile care nu raspund la colestiramina si/sau rifampicina **(III)**
d) plasmafereza sau dializa hepatica pentru cazurile cu prurit sever care nu raspund la tratament medicamentos **(III)**
e) transplant hepatic **(III)**

3.1.2.5. Tratamentul complicatiilor

Principalele complicatii ale CBP sunt:

- hipertensiunea portala (HTP)
- hiperlipemia
- osteoporoza
- cancerul hepatic

3.1.2.5.1. Hipertensiunea portala

- examen endoscopic anual pana la aparitia varicelor **(II B, C)**

- profilaxia HDS conform ghidului Baveno IV atunci cand varicele au aparut sub tratament cu betablocante
- profilaxia recidivelor hemoragice conform ghidului Baveno IV cu betablocante si ligatura (de preferat) sau sclerozare a varicelor esofagiene

3.1.2.5.2. Osteoporoza

- suplimentarea aportlui de calciu si vitamina D **(IIC)**
- gimnastica si reducerea sedentarismului **(IIC)**
- terapie substitutiva estrogenica cu produsi naturali aplicati transdermic (IIC)
- bifosfonati **(III)**

3.6. Transplantul hepatic

Indicatia de transplant este codificata de scorul de risc Mayo si de nivelul bilirubinei. In plan clinic indicatia de transplant este data de

- insuficienta hepatica **(IIA)**
- prurit sever intratabil **(III)**
- osteoporoza severa **(III).**

3.7. Situatii speciale

3.7.1. Sarcina

(a) Terapia specifica (UDCA) trebuie oprita/amanata la pacientele ce doresc o sarcina. Tratamentul cu UDCA pare sa fie sigur in ultimul trimestru de sarcina la pacientele cu colestaza **(III).**

(b) Pentru pacientele cu varice esofagiene trebuie initiate terapia cu betablocante. Faza a doua a travaliului trebuie limitata ca durata **(III).**

Bibliografie

1. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med 2005;353:1261-1273
2. Ishibashi H, Komori A, Shimoda S, Gershwin ME. Guidelines for therapy of autoimmune liver disease. Semin Liver Dis 2007;27(2):214-226
3. Gershwin ME, Ansari AA, Mackay IR. Primary biliary cirrhosis : an orchestrated immune response against epithelial cells. Immunol Rev 2000; 174:210-25
4. Selmi C, Balkwill DL, Inverzinni P. Patients with primary biliary cirrhosis reat against a ubiquitous xenobiotic metabolizing bacterium, Hepatology 2003; 38:1250-7
5. Leung PS, Quan C, Park O. Immunization with a xenobiotic 6-bromohexane bovine serum albumin conjugate induces antimitochondrial antibodies. J Immunol 2003;170:5326-32
6. Jazzawi RP, Caestecker JS, Goggin PM, Britten AJ, Joseph AEA, Maxwell JD, Northfield TC. Kinetics of bile acid handling in cholestatic liver disease: effect of ursodeoxycholic acid. Gastroenterology 1994;106:134-142