Liver diseases in the older adult

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Abstract

Although there are no liver diseases specific to advanced age, the clinical course and management of liver disease in the older adult may differ from those in younger people. Changes in hepatic morphology with aging may lead to changes in liver function. Disturbances in laboratory liver function tests are similar as in younger people and should lead to the same vigilance in investigating for liver disease. Changes in immune function lead to more symptomatic acute hepatitis A, more progression to chronicity in hepatitis B and more fibrosis progression in chronic hepatitis C, especially after liver transplantation with livers from older donors. Treatment for chronic hepatitis C or autoimmune hepatitis is similar for younger or older adults, but side effects may be more prominent in older people. Comprehensive geriatric assessment should be part of the preliminary evaluation of the older patient with liver disease. (Acta gastroenterol. belg., **2010**, 73, **1-4**).

Key words : aging, liver disease, older adults, viral hepatitis, liver surgery, liver transplantation.

Introduction

One of the most important socio-economic phenomena in the 20th and 21st centuries is the growing number of older people not only in industrialized countries but worldwide. With increasing age several physiological functions gradually decline (1). In the past, the liver was considered to be remarkable for the absence of any major age-related alteration (2). However, recently changes in hepatic histology with old age have been identified, probably contributing to age-related changes in liver function. Although there are no liver diseases specific to advanced age, the clinical course and management of liver diseases in the older adult may differ in several aspects from those in younger adults.

Pathophysiology of aging in the liver

Several theories have been advanced to explain aging of the liver. A progressive degeneration of the genetic material by mutations leads to accumulation of non-functional proteins characterized by lipofuchsine storage in the liver. According to another theory, accumulation of mutations in the mitochondrial DNA induces a reduction in synthesis of enzymes of the respiratory chain leading to accumulation of reactive oxygen species. These may enhance the inflammatory responses and fibrogenesis induced by environmental factors as alcohol, obesity, drugs or storage disease (3). A theory that becomes progressively more endorsed in explaining aging is the 'mitotic clock' of the telomeres. Telomeres are repetitive hexameric sequences at the extremities of the chromosomes measuring 5-15 kb. With each mitosis telomeric sequences are lost as the DNA polymerase cannot replicate the distal extremities of the chromosomes (end replication problem). This shortening of the telomeres leads to incapacity of the cell to divide (senescent cell) (4). Telomerase is a ribonucleoprotein that can stabilize the telomere length. Its activity is reduced in syndromes of premature aging. In the liver an increased number of senescent cells is seen in older people, but also in chronic hepatitis C and hepatocellular carcinoma (HCC) (5). Chronic hepatitis C could accelerate telomeric shortening, what can be an explanation for the severity of the infection in the older individual where already many senescent cells are present.

Morphological and biochemical changes in the aging liver

Liver volume and blood flow decrease with age independently from the decrease in body weight (6). The number of hepatocytes seems to diminish (7). There is an increase in size of the lysosomes with accumulation of lipofuchsine, end product of lipid peroxidation (8). Finally, the smooth endoplasmic reticulum is reduced related to a decrease of microsomal enzymes (9). At the level of the liver sinusoids a pseudocapillarization is seen, including thickening and defenestration of the liver sinusoidal endothelial cell and deposition of collagen and basal lamina in the extracellular space of Disse (10). The functional implication is reduced sinusoidal perfusion which will impair the hepatic clearance of highly extracted substrates.

Biochemical liver tests do not change substantially with age (11). This means that in older patients disturbances of biochemical tests also point to liver disease.

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Modification of expression and management of liver diseases in older adults.

Older people have an increased risk for disease-specific mortality and are at higher risk for treatment-associated morbidity than younger persons. However, older patients who are in good health tolerate commonly used treatment regimens as well as younger patients. Chronologic age alone is an inadequate predictor of treatment tolerance and benefit in the heterogeneous older population. A diagnosis of liver disease in an older person is likely to be made in the context of that individual's pre-existing health problems, which introduces very important issues in clinical decision making and treatment. Multiple issues associated with aging impact liver disease management, including functional impairment, co-morbidity, social support, cognitive function, psychological state, and financial stress. Evaluation of the co-morbidity in an older person newly diagnosed with liver disease and assessment of the severity of the various pre-existing conditions and their overall and individual impact on the course of the disease are crucial to providing quality care to older individuals. In this respect a multidisciplinary approach might be useful in the management of the geriatric patient with liver disease. Comprehensive Geriatric Assessment (CGA) should be part of the routine preliminary evaluation of the older patient with liver disease (12). This would help to identify patients with both adverse function and prognosis. Doing so, this may lead to an optimalization of the strategy for the management of liver problems in older people.

Hepatitis A

Acute hepatitis A is usually asymptomatic in children. Middle-aged and older patients generally have more severe hepatitis A virus (HAV) infection and may experience serious complications. Case fatality rates have been estimated to be less than 1% for children and young adults, raising to 2.5% in individuals older than 50 years (13). The reason for this may be multifactorial : the ability to recover may be impaired by a higher prevalence of comorbid conditions, decline in immune function, and slower regenerational capacity of the liver.

The number of individuals lacking immunity is increasing in the Western countries, even in older subjects (14). Older patients who have chronic liver disease and who do not have anti-HAV should be vaccinated including those awaiting liver transplantation (15).

Hepatitis B

In the Western countries, older patients usually are exposed less to risk factors for hepatitis B virus (HBV) transmission (sexual, intravenous drug use). Acute hepatitis is rare. However, the cases that occur seem to have a higher risk for progression to chronic infection (16,17), most probably due to changes in the immune system with aging. This hypothesis is confirmed by poor response of older adults to HBV vaccination (18).

Hepatitis C

Several studies have shown that age at infection is a main risk factor for fibrosis progression in chronic hepatitis C, being highest in those infected at 50 years of age or older (19,20). The reason is unknown, but may be related to the decline in immune function with age.

Currently, the standard care for chronic hepatitis C virus (HCV) infection is pegylated interferon and oral ribavirin. In the registration studies, older age was an independent predictor of poor response (21,22). These studies, however, excluded patients over 65 years and comorbidities frequently seen in older patients. Studies on treatment of HCV in older patients are few. In a study, 33 naïve patients with chronic hepatitis C with mean age of 70.2 ± 1.2 years were treated with pegylated interferon α-2b (1.5 μg/kg/week) plus ribavirin and compared to a younger adult group matched for sex, genotype, viral load and histology (23). The results indicate that older patients have significant more side effects and lower rate of sustained viral response (SVR). Cost-benefit analysis showed that only selected patients aged ≥ 65 years should be treated. Nudo *et al.* (24) comparing 30 patients older than 60 years with 41 control patients younger than 60 years, report no significant differences in SVR after treatment with interferon, interferon plus ribavirin or pegylated interferon plus ribavirin. However, patients older than 60 years were more likely to develop anemia, neutropenia and thrombocytopenia while on treatment. Older patients are also at risk of neurological side effects of interferon (confusion, lethargy, cognitive changes and depression) (25). The current guidelines on management of hepatitis C do not stipulate an upper age limit for antiviral treatment (26-28). However, treatment in the older patients remains controversial, and in practice older patients are less often considered and referred for treatment. The decision on treatment should be individualized, taking into account the physiological age and comorbidities.

Drug-induced hepatitis

Biotransformation of drugs in the hepatocytes depends on blood flow reaching the liver, uptake of the substance in the cell and metabolisation. As hepatic blood flow is decreased, the hepatic uptake may be impaired due to changes in the sinusoidal endothelium and cytochrome P-450 activity is reduced in the elderly ($>$ 70 y), older patients may be more susceptible to drug-induced liver disease (29). Drugs for which age has been demonstrated to predispose to hepatotoxicity are halothane (30), isoniazid (31), amoxycillin-clavulanate (32) and paracetamol, the latter especially in frail older patients (33). Most drugs are not more hepatotoxic in older adults. It has to be considered, however, that older patients have higher rates of polypharmacy and their risk

for drug-induced hepatotoxicity is correspondingly elevated.

Alcoholic liver disease

Alcohol consumption misuse remains an important public health problem in old age (34). The risk of alcoholic liver disease is related to the daily quantity of alcohol consumed and the duration of the intake. It is obvious that age plays a role, as well as cofactors such as obesity and genetic factors. Studies from the US and UK show that alcoholic cirrhosis is most prevalent in patients between 70 and 80 years old (35,36).

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a clinicopathological spectrum of liver abnormalities ranging from steatosis to non-alcoholic steatohepatitis (NASH). Part of the patients with NASH will develop advanced fibrosis and cirrhosis. Age ($>$ 45 years) with obesity, diabetes mellitus and AST/ALT $>$ 1 have been identified as predictors of liver fibrosis (37). It is now clear that a large proportion of cases with cryptogenic cirrhosis represent the end stage of NASH (38). Cases of cryptogenic cirrhosis in old age may be due to metabolic risk factors developing in adult life.

Autoimmune hepatitis

Autoimmune hepatitis used to be considered as a disease in young females. Recent studies have shown that patients may not only present between 10 and 30 years of age, but that another peak in presentation occurs between 50 and 70 years of age (39,40). Treatment strategies are identical for all adult ages and outcome is similar in the older and young individuals (40,41). Caution should be used when administering steroids to older patients especially women who may have osteopenia or diabetes.

Primary and secondary malignant liver tumors

Several studies in Western countries seem to indicate that age is a risk factor in development of HCC in cirrhosis, probably reflecting the longstanding cirrhosis (42-44). No significant differences in complications, survival months, intensive care admissions and mortality were reported between age groups receiving liver resection for liver malignancy in a noncirrhotic liver (45), as the overall capability for regeneration is unchanged in older patients. In case of resection for HCC in a cirrhotic liver, the reports are less clear. Increased hospital mortality mainly due to sepsis was reported after selective hepatectomy for HCC in cirrhosis in patients $>$ 70 years (46). Another study, however, did not show significant differences in morbidity, mortality and long-term survival after surgical resection of HCC (47). Careful selection of patients for resective liver surgery and experienced surgical and anesthetical teams are needed to manage these patients (48). Transarterial chemo-embolisation can palliate and prolong survival and seems well tolerated and equally effective in younger or older patients with HCC (49).

Liver transplantation

Liver transplantation is considered an acceptable treatment for selected patients with end-stage chronic liver disease and fulminant liver damage. According to the European Liver Transplant Registry (ELTR), the proportion of adult liver recipients older than 60 years increased from $<$ 10% in 1990 to about 20% in 2008. The survival rate as reported by the ELTR was significantly lower for liver recipients $\geq$ 60 years of age than for recipients $<$ 60 (http://www.eltr.org, accessed 30.12.2009). This shorter survival in older patients is due to several comorbid factors such as cardiopulmonary disease and advanced kidney dysfunction, being in hospital pre-transplantation, having bad liver function as indicated by low albumin, raised bilirubin, raised prothrombin time and a high Child-Pugh score (50).

In view of organ shortage, livers from older donors are more frequently offered. Graft survival is reported to be decreased when the donor is $>$ 60 years old (51). The severity of recurrent hepatitis C is strongly influenced by donor age (52,53). The best survival was reported in patients receiving grafts from donors $<$ 30 years of age. Donor age $>$ 40 was the strongest predictive factor for mortality in patients transplanted for HCV-related cirrhosis (54,55). It seems to be appropriate to avoid livers from older donors for patients with HCV-related end stage liver disease. The allocation policy in Eurotransplant does not always allow to keep with this intention.

References

1. LAMBERT S., VAN DEN BELD A., VAN DER LELY A. The endocrinology of aging. *Science*, 1997, **278** : 418-424.
2. POPPER H. Aging and the liver. *Prog. Liver. Dis*., 1986, **VIII** : 659-683.
3. PARDA M., ROBINO G. Oxidative stress-related molecules and liver fibrosis. *J. Hepatol.*, 2001, **35** : 297-306.
4. TAKUBO K., NAKAMURA K., IZUMIYAMA N., FURUGORI E., SAWABE M., ARAI T., ESAKI Y., MAFUNE K., KAMMORI M., FUJIWARA M., KATO M., OSHIMURA M., SASAJIMA K. Telomere shortening with aging in human liver. *J. Gerontol. A. Biol. Sci. Med. Sci.*, 2000, **55** : 533-536.
5. PARADIS V., YOUSSEF N., DARGÈRE D., BÂ N., BONVOUST F., DESCHATRETTE J., BEDOSSA P. Replicative senescence in normal liver, chronic hepatitis C, and hepatocellular carcinomas. *Hum. Pathol.*, 2001, **32** : 327-332.
6. WYNNE H., COPE L., MUTCH E. *et al*. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology*, 1989, **9** : 297-301.
7. CHAN C.H. The aging liver. *In* : TEXTER (ed). The aging gut. Masson, New York, 1983, pp. 21-26.
8. IKEDA H., TAUCHI H., SATO T. Fine structural analysis of lipofuscin in various tissues of rats of different ages. *Mech. Ageing Dev.*, 1985, 33 : 77-93.
9. SCHMUCKER D.L. Liver function and phase I drug metabolism in the elderly : a paradox. *Drugs Aging,* 2001, **18** : 837-851.
10. LE COUTEUR D.G., FRASER R., COGGER V.C., MCLEAN A.J. Hepatic pseudocapillarization and atherosclerosis in ageing. *Lancet*, 2002, **359** : 1612-1615.
11. TIETZ N.W., SHUEY D.F., WEKSTEIN D.R. Laboratory values in fit aging individuals – sexagenariabns through centenarians. *Clin. Chem.,* 1992, **38** : 1167-1185.

12. ABELLAN VAN KAN G., ROLLAND Y., BERGMAN H., MORLEY J.E., KRITCHEVSKY S.B., VELLAS B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *J. Nutr. Health Aging*, 2008, **12** : 29-37.
13. WILLNER I.R., UHL M.D., HOWARD S.C., WILLIAMS E.Q., RIELY C.A., WATERS B. Serious hepatitis A : an analysis of patients hospitalized during an urban epidemic in the United States. *Ann. Intern. Med.*, 1998, **128** : 111-114.
14. THIERFELDER W., MEISEL H., SCHREIER E., DORTSCHY R. Die Prävalenz von Antikörpern gegen Hepatitis A, Hepatitis B, und Hepatitis C-viren in der deutschen Bevölkerung. *Gesundheitswesen*, 1999, **61** : 110-114.
15. CDC. Prevention of hepatitis A through active or passive immunization : recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, 1999, 48 (No RR-12) : 1-37.
16. KONDO Y., TSUKADA K., TAKEUCHI T., MITSUI T., IWANO K., MASUKO K., ITOH T., TOKITA H., OKAMOTO H., TSUDA F., MIYAKAWA Y., MAYUMI M. High carrier rate after hepatitis B virus infection in the elderly. *Hepatology*, 1993, **18** : 768-774.
17. CHIARAMONTE M., FLOREANI A., NACCARATO R. Hepatitis B virus (HBV) in the elderly : an underestimated problem ? *Biomed. Pharmacother.*, 1987, **41** : 121-123.
18. DENIS F., MOUNIER M., HESSEL L., MICHEL J.P., GUALDE N., DUBOIS F., BARIN F., GOUDEAU A. Hepatitis-B vaccination in the elderly. *J. Infect. Dis.*, 1984, **149** : 1019.
19. ROUDOT-THORAVAL F., BASTIE A., PAWLOTSKY J.M., DHUMEAUX D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease : a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. *Hepatology*, 1997, **26** : 485-490.
20. POYNARD T., RATZIU V., CHARLOTTE F., GOODMAN Z., MCHUTCHISON J., ALBRECHT J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J. Hepatol.*, 2001, **34** : 730-739.
21. MANNS M.P., MCHUTCHISON J.G., GORDON S.C., RUSTGI V.K., SHIFFMAN M., REINDOLLAR R., GOODMAN Z.D., KOURY K., LING M., ALBRECHT J.K. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomised trial. *Lancet*, 2001, **358** : 958–965.
22. FRIED M.W., SHIFFMAN M.L., REDDY K.R., SMITH C., MARINOS G., GONÇALES F.L. JR, HÄUSSINGER D., DIAGO M., CAROSI G., DHUMEAUX D., CRAXI A., LIN A., HOFFMAN J., YU J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.*, 2002, **347** : 975-982.
23. FLOREANI A., MINOLA E., CARDERI I., FERRARA F., ROSA RIZZOTTO E., BALDO V. Are elderly patients poor candidates for pegylated interferon plus ribavirin in the treatment of chronic hepatitis C ? *J. Am. Geriatr. Soc*., 2006, **54** : 549-550.
24. NUDO C.G., WONG P., HILZENRAT N., DESCHÊNES M. Elderly patients are at greater risk of cytopenia during antiviral therapy for hepatitis C. *Can. J. Gastroenterol.*, 2006, **20** : 589-592.
25. MARCUS E.L., TUR-KASPA R. Viral hepatitis in older adults. *J. Am. Geriat.r Soc*., 1997, **45** : 755-763.
26. MICHIELSEN P., BRENARD R., BOURGEOIS N., DE GALOCSY C.H., DELWAIDE J., HENRION J., HORSMANS Y., NEVENS F., REYNAERT H., ROBAEYS G., SPRENGERS D., VAN VLIERBERGHE H. Steering Committee Belgian Association for the Study of the Liver.Hepatitis C : screening, treatment and prevention practical guidelines. *Acta Gastroenterol. Belg*., 2003, **66** : 15-19.
27. Asian Pacific Association for the Study of the Liver (APASL) Hepatitis C Working Party, MCCAUGHAN G.W., OMATA M., AMARAPURKAR D., BOWDEN S., CHOW W.C., CHUTAPUTTI A., DORE G., GANE E., GUAN R., HAMID S.S., HARDIKAR W., HUI C.K., JAFRI W., JIA J.D., LAI M.Y, WEI L., LEUNG N., PIRATVISUTH T., SARIN S., SOLLANO J., TATEISHI R. Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. *J. Gastroenterol. Hepatol*., 2007, **22** : 615-633.
28. GHANY M.G., STRADER D.B., THOMAS D.L., SEEFF L.B. AASLD Practice Guidelines. Diagnosis, management and treatment of hepatitis C : an update. *Hepatology*, 2009, **49** : 1335-1374.
29. JANSEN P. Liver disease in the elderly. *Best Pract. Res Clin. Gastroenterol*., 2002, **16** : 149-158.
30. NEUBERGER J., WILLIAMS R. Halothane anaesthesia and liver damage. *B. Med. J.*, 1984, **289** : 136-1139.
31. LARREY D., CHAPOUTOT C. Les hépatites et les atteintes des voies biliaires dues à l'amoxicilline-acide clavulanique. *Hepato-Gastro*, 1998, **5** : 45-52.
32. MADDREY W.C. Isoniazid-induced liver disease. *Semin Liver Dis.*, 1981 ; **1** : 77-84.
33. WYNNE H., COPPE L., HERD B. The association of age and frailty with paracetamol conjugation in man. *Age and Ageing*, 1990, **19** : 419-424.
34. ADAMS W.L., COX N.S. Epidemiology of problem drinking among elderly people. *Int. J. Addict.*, 1995, **30** : 1693-1716.
35. GARAGLIANO C.F., LILIENFELD A.M., MENDELOFF A.J. Incidence rates of liver cirrhosis and related diseases in Baltimore and selected areas of the United States. *J. Chronic. Dis.,* 1979, **32** : 543-554.
36. POTTER J.F., JAMES O.F. Clinical features and prognosis of alcoholic liver disease in respect of advancing age. *Gerontology*, 1987, **33** : 380-387.
37. ANGULO P., KEACH J.C., BATTS K.P., LINDOR K.D. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology*, 1999, **30** : 1356-1362.
38. NEUSCHWANDER-TETRI B.A., CALDWELL S.H. Non-alcoholic steatohepatitis : summary of an AASLD single topic conference. *Hepatology*, 2003, **38** : 420-427.
39. SCHRAMM C., KANZLER S., MEYER ZUM BUSCHENFELDE K.H., GALLE P.R., LOHSE A.W. Auto-immune hepatitis in the elderly. *Am. J. Gastroenterol.*, 2001, **96** : 1587-1591.
40. VERSLYPE C., GEORGE C., BÜCHEL E., NEVENS F., VAN STEENBERGEN W., FEVERY J. Diagnosis and treatment of autoimmune hepatitis at age 65 and older. *Aliment Pharmacol. Ther.*, 2005, **21** : 695-699.
41. AL-CHALABI T., BOCCATO S., PORTMANN B.C., MCFARLANE I.G., HENEGHAN M.A. Autoimmune hepatitis (AIH) in the elderly : a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed in a tertiary referral centre. *J. Hepatol.*, 2006, **46** : 575-583.
42. DEL OLMO J.A., SERRA M.A., RODRIGUEZ F., ESCUDERO A., GILABERT S., RODRIGO J.M. Incidence and risk factors for hepatocellular carcinoma in 967 patients with cirrhosis. *J. Cancer Res. Clin. Oncol.*, 1998, **124** : 560-564.
43. MURAKAMI C., HINO K., KORENAGA M., OKAZAKI M., OKUDA M., NUKUI K., OKITA K. Factors predicting progression to cirrhosis and hepatocellular carcinoma in patients with transfusion-associated hepatitis C virus infection. *J. Clin. Gastroenterol.*, 1999, **28** : 148-152.
44. COLLIER J.D., CURLESS R., BASSENDINE M.F., JAMES O.F. Clinical features and prognosis of hepatocellular carcinoma in Britain in relation to age. *Age Ageing,* 1994, **23** : 22-27.
45. ETTORRE G.M., SOMMACALE D., FARGES O., SAUVANET A., GUEVARA O., BELGHITI J. Postoperative liver function after elective right hepatectomy in elderly patients. *Br. J. Surg*., 2001, **88** : 73-76.
46. YANAGA K., KANEMATSU T., MATSUMATA T., YOSHIDA Y., SUGIMACHI K. Hepatic resection for hepatocellular carcinoma in elderly patients. *Am. J. Surg.*, 1988, **155** : 238-241.
47. POON R.T., FAN S.T., LO C.M., LIU C.L., NGAN H., NG I.O., WONG J. Hepatocellular carcinoma in the elderly : results of surgical and nonsurgical management. *Am. J. Gastroenterol.*, 1999, **194** : 2460-2466.
48. BISMUTH H. Hepatocellular carcinoma in the elderly : results of surgical and nonsurgical management. *Am. J. Gastroenterol.*, 1999, **94** : 2336-2337.
49. EL-SERAG H., SIEGEL A., DAVILA J., SHAIB Y.H., CAYTON-WOODY M., MCBRIDE R., MCGLYNN K.A. Treatment and outcomes of treatment of hepatocellular carcinoma among Medicare recipients in the United States : a population based study. *J. Hepatol.*, 2006, **44** : 158-166.
50. COLLINS B., PIRSCH J., BECKER Y., HANAWAY M.J., VAN DER WERF W.J., D'ALESSANDRO A.M., KNECHTLE S.J., ODORICO J.S., LEVERSON G., MUSAT A., ARMBRUST M., BECKER B.N., SOLLINGER H.W., KALAYOGLU M. Long-term results of liver transplantation in patients 60 years of age and older. *Transplantation*, 2000, **70** : 780-783.
51. FENG S., ROBERTS J. An older liver in the hand or a (possibly) younger liver in the bush ? *Am. J. Transpl.*, 2005, **5** : 425-427.
52. BERENGUER M., PRIETO M., SAN JUAN F., RAYON J., MARTINEZ F., CARRASCO D., MOYA A., ORBIS F., MIR J., BERENGUER J. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology*, 2002, **36** : 202-210.
53. BERENGUER M. Recurrent allograft disease : viral hepatitis. *Acta Gastroenterol. Belg.*, 2005, **68** : 337-346.
54. WALI M., HARRISON R., GOW P., MUTIMER D. Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C. *Gut*, 2002, **51** : 248-252.
55. MACHICAOV, BONATTI H., KRISHNA M., AQUEL B., LUKENS F., NGUYEN J., ROSSER B., SATYANARAYANA R., GREWAL H., HEWITT W., HARNOIS D., CROOK J., STEERS J., DICKSON R. Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation*, 2004, **77** : 84-92.