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Management of HCV Infection in the Elderly

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http://dx.doi.org/10.5772/55314

1. Introduction

During the past decade, the knowledge of clinical course and management of hepatitis C virus (HCV) infection has increased enormously, but there are few data on the course of the disease and its treatment in the elderly population (age > 60 years). According to its epidemiology, we are now facing HCV infection from the 20th century. We must take into account that in contrast to a younger population, old people who will develop Chronic C Hepatitis will be mainly women with genotype 1 and more severe fibrosis as clinical presentation pattern.

Thus, chronic infection is prevalent and may be severe in older population. Moreover, aging is an adverse factor for liver disease progression and treatment outcome.

2. Hepatitis C in elderly

Among younger people HCV infection declines [1]. HCV infections are common worldwide. It is estimated that about 3% of the world's population have HCV. There are about 4 million carriers in Europe alone. The prevalence of HCV in the general population varies widely across European countries, with ranges from 0.4% in Sweden, Germany and the Netherlands to over 20% in one region of Italy. According to an American National Health survey, the prevalence of HCV infection in elderly population varies from 0,9 % to 1.0% in subjects who were, respectively, in the age groups of 60-69 years and 70 years and more [2]. In general, countries in the southern part of Europe have a higher HCV prevalence compared to countries in the north or west of the EU. Italy in particular has a high general population prevalence of HCV, much higher than the country's estimated HBV prevalence [3]. In a large Italian study conducted among 1646 subjects, seroprevalence of HCV antibodies were found between 5% and 2% in patient ranging respectively, 58 to 67 years and 68 to 77 years [4].

Epidemiologic and phylogenetic assessments suggest this is caused by a period of increased iatrogenic transmission that took place around the 1960s due to the exposure to blood or blood products mainly deriving from using of non-disposable syringe [3, 5]. Subsequently, HCV infection is mainly due to risky behaviour, including tattooing, piercing, and sharing contaminated syringes among drug users. Finally, the rate of new infections decreased in the 1990s with the introduction of anti-HCV blood testing.

Hence, because chronic liver disease may develop many years after acute HCV infection, the past incidence of acute infections is a major determinant of the future burden of HCV-associated complications. Projections of the future prevalence of HCV-infected patients showed that, although the prevalence of HCV infection may be currently declining because of the decline in incidence in the 1990s, the number of persons infected for the next 20 years could increase substantially before peaking in 2015 [6].

If the incidence of new HCV infections does not increase in the future, persons born between 1940 and 1965 will be at highest lifetime risk of acquiring the infection [6]. To date, the true prevalence of HCV infection among elderly residing in nursing homes is largely underestimated; thus, data from a prospective study demonstrated a high seroprevalence (4,5%) in such population [7].

3. Natural history and age-related aspects

Given the statement above, we expect an increasing burden of decompensated cirrhosis and hepatocellular carcinoma (HCC) for the next two decades [1]. People who develop acute hepatitis C ignore this fact, so recognizing that disease onset is usually based on the potential circumstance of exposure. Progression into the chronic hepatitis is conventionally defined as persistence of increased levels of the aminotransferases for 6 months or, more appropriately, by the confirmation of HCV in the blood beyond that time period. The rate of persistence of HCV virus after an acute infection varies between several studies [8-11] but, in general, the HCV-RNA positivity is about 2,5-fold higher in old people than in person aged < 20 years [2]. Evolution from acute to chronic hepatitis mainly occurs in the absence of clinical manifestations that become clear only after the liver functions are significantly compromised. Decompensation of cirrhosis may occur soon or, more usually, several years after cirrhosis is recognized [12].

However it has been demonstrated in a cohort of patient with a known history of single blood transfusion in the past, that the period between the age at supposed infection and the development of cirrhosis was shorter if the infection was acquired at an older age [13]. The average period between the age of infection and the onset of cirrhosis was 33 years in patients who acquired the HCV infection at the age of 21 to 30, and was reported to decrease to 16 years in patients who acquired the infection after the age of 40 [13, 14]. Similar findings were demonstrated in a Japanese study: the mean time in developing cirrhosis in patients who had a blood transfusion at the age of 50 or older was reported to be 9.8 years, whereas were 23.6 years in patients who had a blood transfusion before 50 years [15]. The same study also demonstrated

that the mean time in developing HCC was 31.5 years against 14.7, depending from receiving blood transfusion respectively, before or after 50 years [15].

Moving from both findings, we can deduce that when HCV infection is acquired at an old age, it turns more rapidly into an advanced liver disease, including developing of HCC. Thus, it has been demonstrated that both patient with chronic HCV infection and HCV-related cirrhosis will develop an HCC in 1% to 2% of cases per year [3]. In contrast with younger people, acquiring HCV infection at older age means that complications of cirrhosis, such as ascitic decompensation, fibrosis and HCC, are often the initial manifestations of hepatitis.

Furthermore, the conjunction of old age at infection, long duration of infection, and aging, results in a higher risk of rapid fibrosis progression [16]. Liver fibrosis is more pronounced in elderly than in young people. A study conducted on 6865 patients older than 65 ys demonstrated a significant association with age and more intense fibrosis at liver biopsy, regardless of the duration of infection. Such results corroborate previous modelling, identifying the major role of aging as an accelerating factor for fibrosis progression after an age of 50 ys [16]. Authors raised several hypotheses to explain why HCV infection during aging is associated to enhanced liver fibrogenesis. Animal studies demonstrate in aging liver enhanced hepatic necrosis with a subsequent exacerbated free radical production and oxidative stress and enhanced susceptibility of senescent hepatic stellate cells to fibrogenetic stimuli.

Aging is undoubtedly associated with a higher susceptibility to environmental factors, reduction in the rate of hepatic blood flow and reduced mitochondrial capacity [17]. The association of Nonalcoholic fatty liver disease (NAFLD) and old age is also a factor that may contribute to the reduction of mitochondrial reserve, leading to liver deficiency in the presence of triggering events, such as HCV infection [18]. Taking into account the comorbidity and polypharmacology of the elderly patient, a good explanation might consider such conditions as contributor factors both in accelerating liver fibrosis and declining liver function.

Finally, it must also be outlined that immune system function declines with age [19, 20] and may be responsible for overreaction against HCV infection. With aging, virus T-cell immuno-mediated response is impaired due to both a decrease of T-cell function and the ability in recognizing new antigens [21]. Furthermore, memory subsets T-cell are reduced and cytokine profile is shifted from Th1 to Th2 leading to a pro-inflammatory response against the antigens [22, 23]. To sum up, such phenomena belong to the so-called immunosenescence that undoubtedly affects both the severity of liver inflammation and the efficacy of Interferon-based therapies.

4. HCV treatment in the elderly

The clinical course and management of liver disease in the elderly may differ in several aspects from those of younger adults. Comorbidities are the main culprits that render elderly patients more vulnerable to poor drug compliance. Therefore, physicians assign such patients to a lower priority treatment group, notwithstanding they need treatment since their infection

advances rapidly. However, this issue is becoming of interest in countries such as Japan and Italy, where the average age of patients who receive antiviral therapy is about 10-15 years older than other countries [4, 24].

The efficacy and safety of treating elderly patients remain on debate. Mortality due to liver failure and HCC is expected to peak after 2030. One way to decrease mortality might be to extend access to current antiviral therapies and to develop more effective antiviral protocols. Despite the predictable epidemiological picture, a very limited number of studies have been dedicated to HCV treatment at old age and most of these have been conducted in the Japanese and Italian population.

Pegylated interferon (Peg-IFN) plus ribavirin combination therapy has led to a marked progress in the treatment of chronic C hepatitis [25-27]. However, in aged patients, the antiviral effect and tolerability to treatment are the main determinants in achieving results [25, 28]. As previously explained, with aging, development of both liver fibrosis and hepatocellular carcinoma has been shown to be faster. Accordingly the first goal of treatment of HCV-infected elderly patients should be HCV elimination [25]. Thus, a treatment strategy, aiming at the improvement of the antiviral efficacy, should be started as soon as possible.

4.1. Screening and initial assessment

According to the American Association for the Study of Liver Disease (AASLD), persons who received transfusion of blood or blood products before July 1992 should be checked for HCV infection [29]. Clinical statements about the opportunity of age-based HCV screening due to it's cost-effective are not clearly defined instead of current risk-based screening practices. However, it is conceivable that people older than 65 year with altera-tions in liver function might be screened for HCV infection even in the absence of known/suspected exposure to HCV.

The diagnosis of chronic hepatitis C is based on the detection of HCV infection (positive anti-HCV antibodies and HCV RNA) in a patient with signs of chronic hepatitis. Rarely, in immunosuppressed patients, anti-HCV antibodies are not detected and HCV RNA is present alone [30]. In order to determine the dose of Ribavirin and treatment decision, the HCV genotype [1-6] can be determined by various methods, including direct sequence analysis, reverse hybridization and genotype-specific real-time PCR [30]. Assessment of the severity of liver disease is recommended before beginning therapy. Liver biopsy, the gold stand-ard and more recently, non-invasive methods, including serological markers and transient elastography (Fibroscan™, Echosens), have been extensively evaluated in patients with chronic HCV infection. The accuracy of non-invasive tests of liver fibrosis is good for identifying patients with mild fibrosis and cirrhosis, but is less reliable for discriminating moderate and severe fibrosis [31].

In any case, according to the geriatric medicine good practice, treatment decisions should be tailored on the basis of the severity of the liver disease and presence of comorbidity. Therapy is contraindicated for patients with decreased life expectancy (< 5 years) due to severe

hypertension, heart failure, or coronary artery disease, poorly controlled diabetes or obstructive lung disease [29].

4.2. Individualised therapy for chronic hepatitis c and future perspectives

According to the European Association for the Study of the Liver (EASL), the primary goal of HCV therapy is to cure the infection, which results in eliminating detectable circulating HCV after cessation of treatment. Sustained virological response (SVR) is defined as an undetectable HCV RNA level (<50 IU/ml) 24 weeks after treatment withdrawal. SVR is generally associated with resolution of liver disease in patients without cirrhosis. The current standard of care (SOC) for the treatment of chronic hepatitis C and HCV-related compensated cirrhosis is the combination of a pegylated IFN and ribavirin.

On the basis of the evidence-based data produced by randomised clinical trials, current treatment guidelines recommend administering this therapy for 48 weeks to patients infected by HCV-1 (HCV-1a or HCV-1b) or HCV-4, and for 24 weeks to those infected by HCV-2 or HCV-3 [30, 32]. The same guidelines recommend stopping antiviral therapy after 12 weeks in HCV-1 or HCV-4 infected patients if their HCV-RNA levels have not decreased by at least 2 log 10 in comparison with baseline on the basis of solid evidence showing that such patients have little or no likelihood of achieving a sustained viral response (SVR) when treated for 48–52 weeks. No similar recommendations have been proposed for patients with HCV-2 and HCV-3 infection [30, 32].

Two pegylated IFN-α molecules can be used in combination with ribavirin (Peg-IFN α-2a or Peg-IFN α-2b). The pharmacokinetics of these compounds differs. A large-scale post-approval US trial comparing various schedules of administration of pegylated interferons with ribavirin in patients infected with HCV genotype 1 showed no significant difference between the tested strategies [30]. In contrast, two Italian trials in patients infected with HCV genotypes 1, 2, 3, and 4 showed some benefit, mostly in genotype 1 patients, in favor of pegylated IFN-α-2a in combination with ribavirin [30, 33, 34]. Although efficacy is still debated, there is currently no conclusive evidence that one pegylated IFN-α should be preferred to the other one as first-line therapy [30].

However, elderly patients with genotype 1 and high HCV loads have a lower SVR rate than younger patients because of higher dose reduction rates and discontinuation rates due to ribavirin-related anaemia and others side effects [35]. Reasons for discontinuation of therapy consisted mainly of anaemia, fatigue, anorexia and depression [35]. In clinical practice, < 15 % of adults treated with interferon and ribavirin discontinue therapy; however, discontinuation rates have been reported to be as high as 30 % and dose reductions are required in >70 % of individuals aged 60 years or older within the first 12 weeks of therapy [1, 36, 37].

The first-line treatment of chronic hepatitis C is based on the use of any of the two pegylated IFN-α available, administered weekly, subcutaneously, and daily oral ribavirin (evidence grading according to GRADE system: A1). Schedules and doses are the same as those recommended for younger patients (GRADE: B3). Pegylated IFN- α-2a should be used at a dose of 180 μg once per week, whereas pegylated IFN- α-2b should be used at a weight-based dose of

1.5 μg/kg per week. The ribavirin dose depends on the HCV genotype. Patients infected with HCV genotypes 1 and 4 should receive a weight-based dose of ribavirin: 15 mg/kg body weight per day. Patients infected with genotypes 2 and 3 can be treated with a flat dose of 800 mg of ribavirin daily, but those with a BMI beyond 25 or who have baseline factors suggesting low responsiveness (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of ribavirin, similar to genotypes 1 and 4 [30].

Very recently, several progresses have been made in the development of new treatments, such as new specific inhibitors or direct antiviral agents that are active against hepatitis C virus. Many studies, mostly conducted in patients infected by HCV genotype 1 who were naïve to the treatment, showed an increase in the SVR rate of 27–31% [38]. Previous relapse patients show very high SVR rates of 75%–86%, while response rates are lower for partial responders (>2 log decline in HCV RNA at 12 weeks of prior therapy) [50–60%) and previous non-responder patients (33%, data only for telaprevir) [38-40]. Even though there are no data demonstrating the efficacy and toxicity of such drugs in elderly population, avoid antiviral therapy due to the advanced age is far from the good practice that should inspire clinicians. Using the antiviral agents in elderly patients undoubtedly requires special attention to co-morbid conditions and tolerance for potential side effects. In conclusion, waiting more clinical studies that will better characterize both the indicators of response and side-effects, we believe that antiviral therapy should be considered in elderly HCV patients with advanced fibrosis. It is important to take into account the life expectancy and co-morbidities in the decision of starting the treatment.

4.3. Treatment monitoring, side effects and stopping rules

According to the EASL Guidelines, patients treated with pegylated IFN-α and ribavirin should be seen at a minimum of weeks 4 and 12 after initiation of treatment, then, at a minimum of every 12 weeks until the end of treatment for both efficacy and side effects, and 24 weeks after the end of therapy to assess the SVR (GRADE: C2). Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels. A sensitive, accurate assay with a broad dynamic range of quantification, ideally a real-time PCR based assay, should be used. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results [30].

Before considering typical side effect related to antiviral therapy some consideration are needed. Elderly have both lower haemoglobin levels and creatinine clearance. Because of a substantial amount of ribavirin is excreted by kidney, elderly with impaired renal function may be carefully followed-up. Ribavirin should not be administrated to patients with a creatinine clearance of < 50 mL/min. Ribavirin should be administered to elderly patients cautiously, starting at lower dosage, with renal function monitored and dosage adjustments made accordingly. Note that, in this population, the serum creatinine level might remain normal as the glomerular filtration rate decreases. Therefore, estimation of creatinine clearance should be done using equations incorporating age as a variable, such as the Cockroft-Gault equation [41].

Furthermore, if Elder have a history of neurological and psychiatric disorders, may be at risk of neurological side-effects of IFN, such as confusion, lethargy, cognitive changes and depression [41]. The most frequent side effect developing after 4–6 weeks of therapy due to the pegylated IFN-α injection, are a flu-like symptoms, which might be easily treated by paracetamol and paying attention to hydration. Severe fatigue, sleeping disorders, skin reactions, depression, irritability and dyspnoea may also be related to IFN therapy. Hematological and biochemical side effects of pegylated IFN-α and ribavirin include neutropenia, anaemia, thrombocytopenia, and ALT flares (Tab. 1). These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4–8 week intervals thereafter [30].

Frequency	IFN-α	Ribavirin
Common	Flu-like symptoms	Haemolysis, dyspepsia
Mild-Uncommon	Depression (mild to severe)	Anaemia
	Anorexia	Myocardial infarction
	Thyroid dysfunction	Angina
	Diabetes	Gastrointestinal symptoms
	Neuropathy	Cough and respiratory symptoms
	Leukocytopenia	Bacterial infections
	Thrombocytopenia	Bone marrow aplasia

Table 1. Most frequent side effect of anti viral therapy.

Most studies report a statistically significant higher ribavirin dose reduction and discontinuation rate in older patients. Based on these data, it would be very interesting knowing whether a close follow-up of the haemoglobin level could allow a better adjustment of the ribavirin dose. This strategy should decrease the discontinuation rate observed in the elderly population and improve the SVR rate. Such approach would take into account the reduction in renal function and the relative lower level of hemoglobin found in elderly, chronic HCV patients, making it possible to adapt the dose in relation to the clinical situation of each patient [42].

The pegylated IFN-α dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, and if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. In individual cases, clinicians may choose to maintain or reduce dosing in these situations but cautious monitoring is advised. When using pegylated IFN-α-2a, the dose can be reduced from 180 to 135 μg/week and then to 90 μg/week. When using pegylated IFN-α-2b, the dose can be reduced from 1.5 to 1.0 μg/kg/week and then to 0.5 μg/ kg/week. Pegylated IFN-α should be stopped in case of marked depression, if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25.000/mm^3. If neutrophil or platelet counts go up, treatment can be re-started, but at a reduced pegylated IFN-α dose. If significant anaemia occurs (haemoglobin <10 g/dl), the dose of ribavirin should be adjusted downward by 200 mg at a time. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dl. Furthermore, treatment should be promptly stopped in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time

of starting treatment) or if a severe bacterial infection occurs at any body site, regardless of neutrophil counts [30, 43, 44].

Recombinant erythropoietin (EPO) and erythropoiesis-stimulating agents (ESAs) can be administered when the haemoglobin level falls below 10 g/dl in order to avoid ribavirin dose reduction or discontinuation (GRADE: C2]. In selected population, such as neoplastic and diabetic patients, ESAs have been linked to increased risk of serious cardiovascular events, tumor progression, thrombosis, and death [45]. Nevertheless, using such drugs may help in managing ribavirin-associated anemia. It is conceivable that clinicians should attend to traditional thrombosis risk factors in patients prescribed ESAs.

Furthermore, it should be noted that there is no evidence that neutropenia during pegylated IFN-α and ribavirin therapy is associated with more frequent infection episodes (GRADE: C1), or that the use of granulocyte colony-stimulating factor (G-CSF) reduces the rate of infections and/or improves SVR rates (GRADE: B1) [30].

Moreover, patients with a history and/or signs of depression should be seen by a psychiatrist before therapy and should be treated with antidepressants (GRADE: C2) [30].

In studies using PEG-IFN plus ribavirin the SVR rate is always significantly lower in older patients than in younger [28, 35, 46]. However SVR depends mainly from HCV genotype. The study of Antonucci confirmed the effect of age in reducing SVR rate in patients infected by HCV 1 or 4 genotypes. Furthermore, such study demonstrated that hepatitis due to HCV genotypes 2 or 3 should be considered for treatment regardless patient's age suggesting that optimal treatment with peginterferon α plus ribavirin may be successfully and safely extended to elderly patients with no major contraindications which should be also included in clinical trials [28].

5. Risk of evolution

Several studies have clearly shown that risk of developing an HCC in those who are untreated is significantly higher than in IFN-treated groups hence, antiviral therapy is an effective way of reducing such risk and improving survival [47-49]. Interestingly, such observations are observed, both, from patients in whom SVR has been observed and a biochemical response obtained.

A retrospective study by Ikeda and colleagues considered the effect of antiviral therapy in a large cohort of elderly patients with HCV hepatitis. Stratifying patients according to their platelet count before therapy (high (> 150.000/mm³), intermediate (100.000 – 149.000/mm³) or low (< 100.000/mm³), authors assessed survival and the risk of hepatocarcinogenesis. The study demonstrated that hepatocarcinogenesis was significantly and inversely correlated with platelet count, reflecting the degree of fibrosis. Interferon treatment for a subgroup of elderly patients with an intermediate or low platelet count conferred substantial advantages with regard to both hepatocarcinogenesis and survival [47, 50]. Furthermore, the study by Ikeda and colleagues demonstrates that platelet count can be used as a simple indicator of the risk

of hepatitis progression. Imai and colleagues, using a conventional interferon-based regimen, found a significantly lower liver-related mortality rate in elderly patients when compared with their untreated counterparts [49].

6. Conclusion

There was no rigorous definition of old age and the upper limit for patient age allowed for interferon-based therapy. Moreover, several aspects should be taken into account; better stratifying elderly population might help physicians in managing HCV infection, regarding life expectancy, cost, side effects, and risks caused by interferon-based therapies (Table 2).

Managing chronic HCV infection in elderly
Identify and treat HCV patients before 60 years or as soon as possible
Carefully assess liver health and weigh the benefits-to-risk ratio of antiviral therapy
Treat HCV 2-3 patients more aggressively because of good response of treatment
Tailor the treatment to each patient
Manage side effect more aggressively

Table 2. Recommendation for managing HCV infection in elderly patients.

Furthermore, current guidelines endorse not to suspend antiviral therapy based exclusively on old age but suggest that special care should be paid to co-morbid conditions and tolerance for potential side effects [31]. Hence, treatment should be initiated under monitoring if there are no major contraindications or severe co-morbidities that would compromise the patient's life expectancy. Moreover, adverse effects typically resolve spontaneously within 2 – 3 weeks of discontinuing therapy.

In any case, treatment for the elderly should be individualized. In conclusion, a reduction in HCC incidence and liver-related deaths are the most desirable endpoints that could be achieved.

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References

[1] Carrion, A. F, & Martin, P. Viral hepatitis in the elderly. Am J Gastroenterol (2012).

[2] Alter, M. J, Kruszon-moran, D, Nainan, O. V, Mcquillan, G. M, Gao, F, Moyer, L. A, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med (1999).

[3] Mchutchison, J. G. Understanding hepatitis C. Am J Manag Care (2004). S, 21-29.

[4] Mazzeo, C, Azzaroli, F, Giovanelli, S, Dormi, A, Festi, D, Colecchia, A, et al. Ten year incidence of HCV infection in northern Italy and frequency of spontaneous viral clearance. Gut (2003).

[5] Chiaramonte, M, Stroffolini, T, Vian, A, Stazi, M. A, Floreani, A, Lorenzoni, U, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer (1999).

[6] Armstrong, G. L, Alter, M. J, Mcquillan, G. M, & Margolis, H. S. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology (2000).

[7] Chien, N. T, Dundoo, G, Horani, M. H, Osmack, P, & Morley, J. H. and Di Bisceglie AM. Seroprevalence of viral hepatitis in an older nursing home population. J Am Geriatr Soc (1999).

[8] Rodger, A. J, Roberts, S, Lanigan, A, Bowden, S, Brown, T, & Crofts, N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. Hepatology (2000).

[9] Alter, M. J, Margolis, H. S, Krawczynski, K, Judson, F. N, Mares, A, Alexander, W. J, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med (1992).

[10] Alter, H. J, Conry-cantilena, C, Melpolder, J, Tan, D, Van Raden, M, Herion, D, et al. Hepatitis C in asymptomatic blood donors. Hepatology (1997). S-33S

[11] Yano, M, Kumada, H, Kage, M, Ikeda, K, Shimamatsu, K, Inoue, O, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology (1996).

[12] Seeff, L. B. Natural history of chronic hepatitis C. Hepatology (2002). S, 35-46.

[13] Mindikoglu, A. L, & Miller, R. R. Hepatitis C in the elderly: epidemiology, natural history, and treatment. Clin Gastroenterol Hepatol (2009). quiz 124

[14] Minola, E, Prati, D, Suter, F, Maggiolo, F, Caprioli, F, Sonzogni, A, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood (2002).

[15] Tong, M. J, Farra, N. S, Reikes, A. R, & Co, R. L. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med (1995).

[16] Thabut, D. Le Calvez S, Thibault V, Massard J, Munteanu M, Di Martino V, et al. Hepatitis C in 6,865 patients 65 yr or older: a severe and neglected curable disease? Am J Gastroenterol (2006).

[17] 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).

[18] Serviddio, G, Bellanti, F, Tamborra, R, Rollo, T, Capitanio, N, Romano, A. D, et al. Uncoupling protein-2 (UCP2) induces mitochondrial proton leak and increases susceptibility of non-alcoholic steatohepatitis (NASH) liver to ischaemia-reperfusion injury. Gut (2008).

[19] Solana, R, & Pawelec, G. Molecular and cellular basis of immunosenescence. Mech Ageing Dev (1998).

[20] Linton, P. J, & Dorshkind, K. Age-related changes in lymphocyte development and function. Nat Immunol (2004).

[21] Pawelec, G, Barnett, Y, Forsey, R, Frasca, D, Globerson, A, Mcleod, J, et al. T cells and aging, January 2002 update. Front Biosci (2002). d, 1056-1183.

[22] Zanni, F, Vescovini, R, Biasini, C, Fagnoni, F, Zanlari, L, Telera, A, et al. Marked increase with age of type 1 cytokines within memory and effector/cytotoxic CD8+ T cells in humans: a contribution to understand the relationship between inflammation and immunosenescence. Exp Gerontol (2003).

[23] Ershler, W. B, & Keller, E. T. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med (2000).

[24] Iwasaki, Y, Takaguchi, K, Ikeda, H, Makino, Y, Araki, Y, Ando, M, et al. Risk factors for hepatocellular carcinoma in Hepatitis C patients with sustained virologic response to interferon therapy. Liver Int (2004).

[25] Oze, T, Hiramatsu, N, Yakushijin, T, Mochizuki, K, Oshita, M, Hagiwara, H, et al. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy. J Hepatol (2011).

[26] Ghany, M. G, Strader, D. B, Thomas, D. L, & Seeff, L. B. and American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology (2009).

[27] Manns, M. P, Mchutchison, J. G, Gordon, S. C, Rustgi, V. K, Shiffman, M, Reindollar, R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet (2001).

[28] Antonucci, G, Longo, M. A, Angeletti, C, Vairo, F, Oliva, A, Comandini, U. V, et al. The effect of age on response to therapy with peginterferon alpha plus ribavirin in a

cohort of patients with chronic HCV hepatitis including subjects older than 65 yr. Am J Gastroenterol (2007).

[29] Strader, D. B, Wright, T, Thomas, D. L, & Seeff, L. B. and American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C. Hepatology (2004).

[30] European Association for the Study of the LEASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol (2011).

[31] European Association of the Study of the LEuropean Association of the Study of the Liver hepatitis C virus clinical practice guidelines. Liver Int (2012). Suppl , 1, 2-8.

[32] Italian Association for the Study of the LItalian Society of Infectious TD, and Italian Society for the Study of Sexually Transmitted D. Practice guidelines for the treatment of hepatitis C: recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting. Dig Liver Dis (2010).

[33] Ascione, A, De Luca, M, Tartaglione, M. T, & Lampasi, F. Di Costanzo GG, Lanza AG, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology (2010).

[34] Rumi, M. G, Aghemo, A, Prati, G. M, Ambrosio, D, Donato, R, & Soffredini, M. F. R. et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology (2010).

[35] Honda, T, Katano, Y, Shimizu, J, Ishizu, Y, Doizaki, M, Hayashi, K, et al. Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. Liver Int (2010).

[36] Iwasaki, Y, Ikeda, H, Araki, Y, Osawa, T, Kita, K, Ando, M, et al. Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. Hepatology (2006).

[37] Tsui, J. I, Currie, S, Shen, H, Bini, E. J, Brau, N, Wright, T. L, et al. Treatment eligibility and outcomes in elderly patients with chronic hepatitis C: results from the VA HCV-001 Study. Dig Dis Sci (2008).

[38] Flisiak, R, & Parfieniuk, A. Investigational drugs for hepatitis C. Expert Opin Investig Drugs (2010).

[39] Poordad, F, & Mccone, J. Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med (2011).

[40] Jacobson, I. M, Mchutchison, J. G, & Dusheiko, G. Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med (2011).

[41] Marcus, E. L, & Tur-kaspa, R. Viral hepatitis in older adults. J Am Geriatr Soc (1997).

[42] Horsmans, Y. Treatment of chronic hepatitis C in elderly patients. Expert Opin Phar-macother (2010).

[43] Hadziyannis, S. J, & Sette, H. Jr., Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med (2004).

[44] Fried, M. W, Shiffman, M. L, Reddy, K. R, Smith, C, Marinos, G, Goncales, F. L, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med (2002).

[45] Sulkowski, M. S, Shiffman, M. L, Afdhal, N. H, Reddy, K. R, Mccone, J, Lee, W. M, et al. Hepatitis C virus treatment-related anemia is associated with higher sustained vi-rologic response rate. Gastroenterology (2010). e1601

[46] Floreani, A, Minola, E, Carderi, I, Ferrara, F, Rizzotto, E. R, & Baldo, V. Are elderly patients poor candidates for pegylated interferon plus ribavirin in the treatment of chronic hepatitis C? J Am Geriatr Soc (2006).

[47] Ikeda, K, Arase, Y, Kawamura, Y, Yatsuji, H, Sezaki, H, Hosaka, T, et al. Necessities of interferon therapy in elderly patients with chronic hepatitis C. Am J Med (2009).

[48] Arase, Y, Ikeda, K, Suzuki, F, Suzuki, Y, Saitoh, S, Kobayashi, M, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Inter-virology (2007).

[49] Imai, Y, Kasahara, A, Tanaka, H, Okanoue, T, Hiramatsu, N, Tsubouchi, H, et al. In-terferon therapy for aged patients with chronic hepatitis C: improved survival in pa-tients exhibiting a biochemical response. J Gastroenterol (2004).

[50] Floreani, A. Hepatitis C: Should antiviral therapy be offered to elderly patients? Nat Rev Gastroenterol Hepatol (2009).