

Hepatitis C treatment in the elderly: New possibilities and controversies towards interferon-free regimens

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Abstract

Due to the progressive aging of the hepatitis C virus

(HCV) population which have acquired the infection during its maximum spread after the Second World War, the management of the elderly HCV-infected patient is emerging as a hot topic. Unfortunately, although it is recognized that the progression of HCV-related liver disease gets faster with aging, and that even extra-hepatic manifestations of HCV infection are probably worse in the elderly, till now, treatment attempts in this population have been significantly limited by the well-known contraindications and side effects of interferon (IFN). The arrival of several new anti-HCV drugs, and the possibility to combine them in safe and effective anti-viral regimens, is relighting the hope of a cure for many elderly patients who had been cut out of IFN-based treatments. However, although these new regimens will be certainly more manageable, it should be underscored that IFN-free doesn't mean free from any contraindication or side-effect. Moreover, one issue which promises to become central is that of the possible interactions between antiviral therapy and the multiple drugs frequently assumed by elderly patients because of comorbidities. In this review, we will revise the epidemiology pointing to HCV as an infection of the elderly, the evidences that HCV harms the health of the aged patient more than that of the young one, and the available experiences of HCV treatment in the elderly with the "old" IFN-based regimens and with the newer drugs. We will conclude that the availability of IFN-free regimens should prompt us to change our mind and consider a significantly larger number of possible candidates among elderly patients, who would take significant advantage from viral eradication. Rather than the anagraphic age, drug-drug interactions and, mainly in case of economic restrictions, an evaluation of life expectancy dependent on liver disease with respect to that dependent on comorbidities, are likely to be the key issues guiding treatment indication in the next future. The sooner we will change our mind with respect to an a priori obstacle for anti-HCV treatment in the elderly, the sooner we will begin to spare many aged HCV patients from avoidable liver-related

complications.

Key words: Hepatitis C virus; Elderly; Interferon; Ribavirin; Telaprevir; Boceprevir; Sofosbuvir; Simeprevir; Daclatasvir; Side effects; Drug-drug interactions

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Core tip: Hepatitis C virus (HCV) infection is a significant threat to the health of elderly patients, in whom liver disease progresses very rapidly and extrahepatic complications affect the quality of life. Till now, treatment attempts have been substantially limited by the side effects of interferon (IFN). Here we discuss how the availability of IFN-free regimens should prompt us to change our mind when assessing treatment indication and to consider a significantly larger number of possible candidates among elderly patients. Drug-drug interactions and assessment of liver disease-dependent vs comorbidities-dependent life expectancy, rather than anagraphic age, are likely to guide the choice of the aged HCV patients to be treated in the next future.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem chronically affecting approximately 170 million people all over the world. Due to the progressive aging of the HCV-infected population, and to the lack of a comparable amount of new cases, the management of the elderly HCV-infected patient is emerging as a hot topic. Old patients are becoming the most representative part of those seen in outpatient clinic visits for hepatitis C and epidemiological data suggest that they will even increase in the next future^[1]. Given this general background, some country-specific differences in the epidemiology of HCV infection can be evidenced and, while the estimated global prevalence of HCV is around 2%^[2], country-specific estimates can vary widely, ranging from less than 1% in United Kingdom and Scandinavia to 15%-25% in Egypt^[3]. Similar average prevalences (1.5%-3.5%) can be observed in vastly different countries, including United States (US), Australia, Spain, Italy and Japan, but with different patterns of age-specific prevalence^[3].

According to the National Health and Nutrition Examination Survey (NHANES), in the US, the peak in age-specific prevalence of anti-HCV antibodies switched from 30-39 to 40-49 years from 1988-1994 to 1999-2002, while the prevalence of HCV-infected

patients was found to be, respectively, 0.9% and 1% in the age groups 60-69 and ≥ 70 years, respectively (lower than the 1.6%-1.8% of prevalence found in the general population)^[4,5]. Indeed, the biggest part of the US HCV patients comes from the population born between 1945 and 1965, who acquired the infection during the 1970s and 1980s from exposure to blood or blood products^[6]. The rate of new infections decreased sharply after the 1990s, with the discovery of HCV and the interventions aimed to control blood products and to reduce the transmission by intravenous drug use^[1]. Although more recent epidemiological data are lacking, according to previous NHANES, it can be speculated that the peak in age-specific prevalence has moved more than ten years forwards, with a consequent significant increase of HCV prevalence in the elderly. A similar age-specific pattern of HCV prevalence can be observed also in Australia and Western and Northern Europe^[7-9].

In countries like Italy, Japan and Egypt, the age-specific distribution of HCV-patients is even more skewed towards old age. Three different studies from Italy found a very high HCV prevalence in the elderly: 11% of 208 patients aged more than 65 years^[10]; 33.1% of subjects aged more than 60 years among a population of 1352 subjects^[11]; 18.2% of subjects in the 60-70 age-group of a population of 681 subjects^[12]. A similar scenario is observed in Japan. In a community-based study, Okayama *et al.*^[13] found that the prevalence of anti-HCV positivity progressively increased with age, reaching 41% in patients aged 80-89 years. Moreover, Sawabe *et al.*^[14] reported 8.8% and 13.1% rates of anti-HCV positivity in in-hospital and autopsy cases older than 60 years, respectively. Even more significant data are available from Egypt: in the largest population-based study, carried out in 2000, HCV prevalence significantly increased with age, peaking at over 60% in the fifth decade and around 40% in subjects older than 60 years, compared to a global prevalence of 24.3%^[15].

Many possible confounding elements should be considered when comparing these different studies and trying to interpret their different results. First of all, for many countries, due to the absence of specific data, estimated prevalences are based on weighted averages for region rather than individual countries, *i.e.*, Northern Europe is the region with the lowest estimated prevalence (< 1%), while Northern Africa has the highest reported prevalence (> 3%)^[3]. Second, well-designed population studies are lacking and available studies often involve populations which are convenient for sampling, such as autopsy or hospital series or blood donors, producing biased estimates of disease burden and exposures. Furthermore, some population studies have been set in rural areas historically exposed to factors that may have locally influenced HCV incidence and for this reason their results could be not representative of the entire country. Third, all available epidemiological studies

have been conducted more than ten years ago, thus they should be interpreted accordingly, in particular when considering age-specific prevalences.

The highest prevalence of HCV infection in the elderly in countries like Italy, Japan and Egypt can be explained only by considering specific factors which led to past peaks of infections. For instance, in Italy, it has been speculated that the widespread use of glass syringes for parenteral treatments after the Second World War could have been responsible for an earlier boost of HCV-infection compared to US^[16]. In Egypt, HCV transmission through blood products and illicit drugs has not represented the major route of infection: indeed, there is consistent evidence for significant transmission through injection therapy, with a particular reference to the parenteral treatment campaign for schistosomiasis, which took place from the 1950s-1960s up to the 1970s^[17]. Of course, injection therapy for Schistosomiasis cannot entirely account for HCV burden in Egypt; however, it's reasonable that it increased the reservoir of HCV in the community, accelerating HCV transmission in the subsequent years even through unconventional routes of infection, such as between spouses^[15]. In Japan, the peak of HCV spread most likely occurred during the turmoil period just after the end of Second World War^[18]. Illicit intravenous drug abuse was highly prevalent at that time in Japanese society and this might have contributed to the horizontal transmission of HCV^[18]. Furthermore, some investigators identified some differences in local medical procedures and folk remedies as possible explanation for unusual areas of high HCV endemicity, which could have had stronger and wider diffusion in the half of the twentieth century and for this reason could have had a role in the peak of HCV incidence in that period^[18].

ESTIMATING THE IMPACT OF HCV INFECTION ON QUALITY AND EXPECTANCY OF LIFE IN ELDERLY PATIENTS

Current guidelines for HCV infection are usually focused on the management of a single disease and this is a barrier for their application in adults with comorbidities^[19]. Indeed, unlike patients usually included in clinical trials, most elderly patients actually have multiple chronic disorders. This is even truer in the case of a systemic disease, as HCV infection should be considered, with interactions between the virus, liver damage and dysmetabolism^[20].

Like other chronic diseases, HCV infection may be associated since its early stages with impairments in health related quality of life, including fatigue, muscle and joint pain, depression, *etc*^[21]. Up to 30 % of HCV patients have psychological disorders, not limited to depression, and up to 67% complain of fatigue^[6,22].

Overall, it is currently well-recognized that HCV-infected patients experience poorer quality of life compared with the general population^[23]. Moreover, it is exactly the elderly population, in which depression and neuropsychological disorders are common, to carry the greater risk for a negative impact of HCV infection on the quality of life. Indeed, by examining a group of patients with chronic hepatitis C by the Fatigue Impact Scale, Hassoun *et al*^[22] found that age was significantly associated with fatigue. Moreover, in another study investigating the incidence of depression in HCV patients undergoing interferon (IFN) treatment, Horikawa *et al*^[24] found that and the only risk factor for depression was advanced age.

To date, major concerns for the management of HCV in elderly patients have been the common side effects of treatment with IFN and ribavirin (RBV), including anemia, neutropenia and thrombocytopenia, which can theoretically trigger cardiac events, and promote infectious disease or hemorrhages. Indeed, a relevant risk of clinically significant cytopenia has been documented in different studies in aged patients, and the rate of discontinuation or dose modification in this population has been frequently greater than 50%^[25,26]. Therefore, when facing an elderly HCV patient, the first question to answer should be whether this patient will progress to liver complications threatening survival and, the second, whether the disease is conditioning or will condition the health-related quality of life.

Poynard *et al*^[27] have examined risk factors for fibrosis progression in chronic hepatitis C and found three independent factors associated with a faster course: age at infection, alcohol consumption (more than 50 g/d) and male gender. The comparison between decades showed that the major acceleration was observed after the age of 50 years, independently from the age at infection and, consequently, from the duration of disease. Therefore, age itself was even more important than duration of infection for predicting the occurrence of cirrhosis^[28]. Also the risk of HCC increases significantly with age, and this is not only dependent on a prolonged duration of infection, since a shorter interval between infection acquired at an older age and the diagnosis of HCC has been demonstrated^[29,30]. The mechanisms underlying this particularly rapid course in the elderly population have not been clearly understood. From experimental studies, it is known that the fibrotic reaction to carbon tetrachloride is greater in older than in younger rats^[31]. The higher vulnerability to environmental factors (especially oxidative stress), the reduction in the rate of hepatic blood flow, the reduced mitochondrial capacity and the impaired immunity are all mechanisms possibly involved in a faster progression of liver damage^[27,32].

Some evidence already exists that treatment can prevent this aggressive progression of HCV infection in elderly patients. In a retrospective study, Arase *et al*^[33] reported that long-term low-dose natural IFN

treatment, without eradicating HCV, was nevertheless effective in preventing hepato-carcinogenesis in aged patients with chronic hepatitis. In another retrospective study analysis of patients older than 60 years, at 5 and 10 years, hepatocarcinogenesis rates were significantly lower in the IFN-treated group, and IFN monotherapy was independently associated with a longer survival in the subgroup with lower platelets (hazard ratio, 2.33, $P = 0.005$)^[34]. Finally, another important issue is that antiviral treatment is associated with improved renal and cardiovascular outcomes in diabetic patients. Indeed, the risk of end stage renal disease, stroke and acute coronary syndrome is significantly reduced in treated patients compared with untreated controls, underlying the systemic impact of the virus^[35]. However, it should be noted that, in contrast with these results, the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) study, the only randomized prospective study carried-on with the aim of verifying the possible benefits from IFN maintenance treatment, showed that low-dose pegylated-IFN (PEG-IFN) therapy for 3.5 years did not reduce the incidence of HCC and the rate of disease progression in CHC patients with bridging fibrosis or cirrhosis who failed to respond to the combination therapy with ribavirin^[36].

Synthesizing, although it is well-known that HCV infection has a negative impact on the quality of life of elderly patients, to date, the complexity of treatment and the lack of supportive data in this age group have significantly limited treatment attempts. Now that the scenario is rapidly changing, and that new IFN-free treatment options are becoming available, the limited but available evidence concerning the benefit of viral eradication in the elderly population should be carefully considered.

AVAILABLE STUDIES ON THE TREATMENT OF HEPATITIS C IN ELDERLY PATIENTS WITH “OLD” DRUGS

Until very recently, the only therapies for the treatment of chronic hepatitis C were based on IFN for all genotypes, either “natural” (human leukocyte-derived) or recombinant (“standard” or PEG). IFN was used as monotherapy at the beginning of the 1990’, in combination with RBV since the beginning of the 21st century and, more recently, and only in patients infected by genotype 1 HCV, with the further addition of a first-generation inhibitor of the HCV NS3 serin-protease [telaprevir (TVR) or boceprevir (BOC)]^[37-40].

Conventional IFN/RBV-based therapies

IFN/RBV-based therapy is typically burdened with numerous adverse events, such as fatigue, fever, myalgias, depression, and severe alterations in blood cells counts, first of all haemolytic anemia and neutropenia^[38,41]. Clinical trials mostly lack data

about tolerance and effectiveness of these therapies in the elderly (in Table 1), data concerning the most significant studies on IFN-based regimens in aged patients are presented, and a comparison with results obtained in younger patients, when available, is reported. Safety appears an important limiting factor for IFN-based therapies in the elderly, mainly because patients more frequently suffer from concurrent chronic cardio-pulmonary diseases. Indeed, it appears that elderly patients have a tendency to obtain lower sustained virological response (SVR) rates compared with younger ones, especially in the case of genotype 1 infection, and that the discontinuation rate due to adverse events is higher. In the study by Antonucci *et al*^[42] on efficacy and safety of PEG-IFN plus RBV in a cohort of HCV patients, patients aged > 40 years with genotype 1 or 4 infection had a significantly lower chance of achieving SVR compared with younger ones (80% vs 32.6%, $P = 0.005$).

Conversely, in another small population of 19 patients aged > 65 years treated with PEG-IFN plus RBV, derived from a larger study on 166 elderly patients, age didn’t seem associated with a reduced virological response and the SVR rate was 42%^[43]. Recently, Frei *et al*^[44] performed a multiple regression model with generalized estimating equations (GEE) to assess the influence of age ≥ 60 years on SVR, taking confounders into account (stage of fibrosis, viral load, genotype, previous treatment, gender). The GEE model showed that age had no significant influence on SVR (OR = 0.91, $P = 0.81$), and that only well-established factors, such as cirrhosis, genotypes 1/4/6 and viral load > 600 000 IU/mL had a negative impact on SVR^[44]. It is also of interest that, in several clinical trials, no association was found between age and SVR in HCV patients with genotypes 2 or 3^[45-47]. Kainuma *et al*^[48] found that, for genotype 1 infection, the discontinuation rate was significantly higher in older patients (42.9% vs 24.4%, $P < 0.001$). A study from Taiwan confirmed that drug discontinuation among elderly patients was significantly higher than among those younger than 65 years (21% vs 6%, $P = 0.001$)^[49]. In a meta-regression analysis conducted by Zhou *et al*^[49] to explore predictors for dose reduction secondary to adverse events in aged HCV patients treated by PEG-IFN plus RBV, the overall incidence of adverse events was 61.3%, and dose reductions due to adverse events was 54.2%. Patients with major dose reductions due to adverse events had a tendency toward a lower likelihood of obtaining SVR, especially in the case of genotype 1. Moreover, incidence of hemolytic anemia due to RBV increases with age and dose reduction or RBV discontinuation are more frequent in patients of ≥ 55 years^[42,43,50]. In a meta-analysis analyzing non-randomized controlled trials on the treatment with PEG-IFN plus RBV in older HCV patients, on intention-to-treat analysis, patients ≥ 65 years (1057) had a significantly lower

Table 1 Studies on conventional interferon/ribavirin-based regimens in aged patients

Author and year	Study design	Number of aged patients treated	Genotype 1/non-1 (available data)	Type of IFN ± RBV	SVR of aged patients vs SVR of younger patients (available data)	Discontinuation or dose reduction of aged patients vs discontinuation or dose reduction of younger patients (available data)
Bresci <i>et al</i> ^[87] , 1993	Prospective	22	NA	IFN-α2b	NA	4 %
Horiike <i>et al</i> ^[32] , 1995	Prospective	19	0/19	IFN-α2a/2b; β-IFN	NA	NA
Van Thiel <i>et al</i> ^[88] , 1995	Prospective	25	Na	IFN-α2b	NA	NA
Alessi <i>et al</i> ^[89] , 2003	Retrospective	50	43/7	IFN-α	18 % vs 20 % <i>P</i> = 0.9	NA
Imai <i>et al</i> ^[90] , 2004	Retrospective	649	NA	IFN (unspecified)	25 % vs 43 % <i>P</i> = 0.03	NA
Iwasaki <i>et al</i> ^[50] , 2006	Prospective	73	50/23 (only 1/2)	IFN α2b + RBV	32 % vs 50 % <i>P</i> = 0.078	77 % vs 38 % <i>P</i> < 0.001
Koyama <i>et al</i> ^[91] , 2006	Prospective	84	35/49	IFN-α2a IFN-α2b	35.7 %	13.1 %
Honda <i>et al</i> ^[92] , 2007 ¹	Prospective	66	54/12	IFN-α2b + RBV	31.8 % vs 38.3 % <i>P</i> = 0.3589	21.2 % vs 14.9 % <i>P</i> = 0.2540
Arase <i>et al</i> ^[93] , 2007 ¹	Prospective	NA (236 all patients)	NA	IFN-α IFN-β	28 %	NA
Tsui <i>et al</i> ^[94] , 2008 ¹	Prospective	35	NA	IFN-α2b + RBV	20 % vs 18.5 % <i>P</i> = 0.79	31 % vs 31 % <i>P</i> = 0.9
Arase <i>et al</i> ^[95] , 2012	Retrospective	33	0/33	IFN-β + RBV	75.8 %	0 %
Zeuzem <i>et al</i> ^[96] , 2004	Prospective	2	0/2	PEG-IFN-α2b	50 %	NA
Nudo <i>et al</i> ^[25] , 2006	Retrospective	30	8/22	IFN IFN + RBV PEG-IFN + RBV	33.3 % vs 51.2 % <i>P</i> = 0.13	53 % vs 34 % <i>P</i> = 0.17
Floreani <i>et al</i> ^[97] , 2006	Prospective	33	NA	PEG-IFN + RBV	45.5 vs 69.7 % <i>P</i> = 0.02	24 % vs 12.2 % NS
Thabut <i>et al</i> ^[43] , 2006	Prospective	166 (281 treatments)	141/104	IFN, IFN + RBV, PEG- IFN alone, PEG-IFN + RBV, RBV alone	IFN 7% RBV 7% Peg-IFN alone 0 % IFN + RBV 16% peg-IFN + RBV 45 %	20 %
Antonucci <i>et al</i> ^[42] , 2007	Retrospective	30	11/19	PEG-IFN + RBV	70 % vs 84 %	16.7% vs 15.8 %
Honda <i>et al</i> ^[26] , 2010	Prospective	115	93/22	PEG-IFN α2b + RBV	37.4% vs 51.5% <i>P</i> = 0.0067	32.2% vs 17.0% <i>P</i> = 0.0003
Gramenzi <i>et al</i> ^[98] , 2010	Cross sectional	34	NA	IFN PEG-IFN + RBV	NA	32 % vs 20 % NS
Kainuma <i>et al</i> ^[48] , 2010	Prospective	314	253/61	PEG-IFN α2b + RBV	31.2 %	36.3 %
Huang <i>et al</i> ^[99] , 2010	Prospective	70	27/43	PEG-IFN α2a + RBV	67.1 % vs 78.6 % <i>P</i> = 0.07	21.4 % vs 6.4 % <i>P</i> = 0.001
Oze <i>et al</i> ^[100] , 2011	Prospective	240	185/55	PEG-IFN α2b + RBV	35.4 %	23.9 %
Ebinuma <i>et al</i> ^[101] , 2001 ¹	Prospective	101	102	PEG-IFN + RBV	41.5% vs 54.3% <i>P</i> = 0.0245	NA
Gramenzi <i>et al</i> ^[102] , 2012	Cross- sectional	378	NA	All types	33 %	NA
Kim <i>et al</i> ^[103] , 2012	Retrospective	38	13/25	PEG-IFN α2a/2b + RBV	65.8 % vs 76.2 % <i>P</i> = 0.15	21.1 vs 9.1 % <i>P</i> = 0.05
Hu <i>et al</i> ^[104] , 2013	Prospective case control	91	56/35	PEG-IFN + RBV	40.7 % vs 61.5 % <i>P</i> = 0.005	14.3 % vs 3 % <i>P</i> = 0.034
Frei <i>et al</i> ^[44] , 2014	Prospective	98	63/35	PEG-IFN + RBV	46.5 % vs 57.2 % <i>P</i> = 0.0970	21.1 % vs 18.4 % NS

¹Elderly defined > 60 years; PEG: Pegylated; IFN: Interferon; RBV: Ribavirin; NA: Not available; NS: Not statistically significant.

likelihood of SVR than those aged < 65 years (42% vs 60.1% respectively, *P* < 0.00001)^[51]. Indeed, the discontinuation rate was significantly higher in older patients than in younger patients (25.5% vs 14.8%,

respectively, *P* < 0.00001), and it was related to adverse events in the aged subgroup (19.2% vs 9.3% respectively, *P* < 0.00001). Also dose modification rates of both PEG-IFN and RBV in patients aged ≥ 65

years were significantly higher than those in younger patients (69.3% vs 55.8% respectively, $P < 0.00001$). Overall, although some conflicting results do exist, it can be concluded that older patients frequently experience adverse events, have a poorer adherence and respond with lower SVR rates to IFN/RBV-based anti-HCV treatments.

Triple therapy with first generation protease inhibitors for genotype 1 HCV infection

In the evolution of anti-HCV treatment regimens, the third step has been the approval of a genotype 1-specific "triple therapy". It consists of a combination of IFN and RBV plus a NS3/4A serine protease-inhibitor, either BOC or TVR, which are direct antiviral agents able to block the life cycle of HCV^[52-57]. However, this treatment can be burdened with severe adverse events and, except for the registrative trials, the clinical experience comes from expanded access programs and urgent prescriptions in real life, being limited to patients with more advanced disease and therefore more prone to adverse events. Among these, hematologic adverse events, such as anemia and leukopenia with infections, are frequently reported^[58]. To note, registrative trials have not included elderly patients, so that there are very few data on safety and efficacy of the triple therapy in this population. Some data can be extrapolated from the two great expanded access programs: the French CUPIC (511 treatment-experienced cirrhotic patients)^[57], and the multicenter, open label, observational study involving TVR therapies in many countries (HEP3002)^[58]. Both were carried out in patients with severe fibrosis or cirrhosis. In the CUPIC study, there were 122 (23.9%) patients aged ≥ 65 and 389 (76.1%) patients aged ≤ 65 . In this large cohort of genotype 1 treatment-experienced cirrhotic patients, a high incidence of serious adverse events (40.0%) and a problematic management of anaemia (erythropoietin and transfusion use in 50.7% and 12.1%, respectively) were observed, severe anemia being more frequent and needing more frequently blood transfusion in older patients^[57,59]. Indeed, among the others, age ≥ 65 years was an independent predictor of anaemia < 8 g/dL or blood transfusions [OR = 3.04 (1.54-6.02), $P = 0.0014$]^[57]. In the HEP3002 study, there were 128 patients ≥ 65 years on an overall of 1782 patients, and 61% of patients ≥ 65 years were cirrhotic (vs 54% in the overall population). Virological outcome didn't seem to depend on age: early rapid virological response was 75% in patients aged ≥ 65 years vs 76% of younger patients, SVR was 76% in treatment naïve patients ≥ 65 years vs 69% in those ≤ 45 years, while it was 39% in prior null responders ≥ 65 years vs 36% in those ≤ 45 years. On the contrary, adverse events were significantly associated with older age: grade 3-4 anemia was present in 45.3% of patients aged ≥ 65 years vs 16.6% of those aged ≤ 45 years; grade 3-4 rash was observed in 2.3% of patients aged ≥ 65

years vs 2.5% of those aged ≤ 45 years; the rate of serious adverse events was 11.7% in patients aged ≥ 65 years vs 2.5% in those aged ≤ 45 years. In a multivariate analysis, age ≥ 65 years was a significant predictor of anaemia [OR = 2.31 (1.46-3.65), $P = 0.0003$], and anti-anemics and blood substitutes were prescribed in 54% of older patients vs 28% of patients in the overall population. However, older age was not significantly associated with discontinuation of telaprevir for adverse events^[60].

Another Japanese study explored the response to triple therapy with TVR in 64 genotype 1b HCV patients aged >60 years compared with 56 patients aged < 60 years^[61]. There were no documented differences in SVR (76.6% vs 83.9%, $P = 0.314$) or in the rate of discontinuation (12.5% for both groups, $P < 0.999$) with the younger population, but only one third of these patients had severe fibrosis. The main adverse events reported in this study were rash, serious skin reactions and anemia. Drug-induced skin disorders were found in 51.6% of the aged patients vs 44.6% of the younger patients, with no significant difference ($P = 0.449$). Instead, there was a significant difference in the occurrence of severe anemia between the two groups. The hemoglobin decrease to 8.5-10 g/dL and < 8.5 g/dL was 40.6% and 50% in the aged group, and 25% and 33.9% in the younger group, respectively ($P = 0.0006$). Another Japanese study analyzed a reduced dose of TVR (1500 mg/day) in 14 patients out of 18 patients > 65 years^[60]. The dose of TVR did not affect SVR, which was 50%. While in the registration trials renal dysfunction was not observed, recent reports suggested that the incidence of renal impairment with TVR and BOC combination therapy may be as high as 5%, more common in old patients, and in those with cirrhosis, diabetes and hypertension. Moreover, by impairing renal function, TVR can increase blood RBV concentration and the plasma/whole blood RBV ratio (49-50). In the study of Rao *et al*^[62], only 1 male patient with cirrhosis in the TVR cohort, aged 75 years, developed a sustained drop in estimated Glomerular Filtration Rate (eGFR) of 40% from baseline; in the BOC cohort, 2 patients, aged 65 and 66 years, both cirrhotics and with normal pre-treatment creatinine levels, were noted to have a self-resolving acute kidney injury. Finally, in the HCV-TARGET consortium of investigators, in order to evaluate the safety profile of BOC and TVR in academic and community centers across the United States, 2212 patients have been enrolled and were at varying stages of treatment. Of 970 patients who started triple therapy regimens (mean age 56 years, range 18-76 years), 74 patients (8%) were aged ≥ 65 , 53 (72%) treated with TVR and 21 (28%) with BOC. Early treatment discontinuation was more common in older compared to younger patients (36% vs 25%, respectively), and was more frequently due to adverse events (48% vs 37%) than to lack of efficacy (22% vs 33%). Anemia, defined as haemoglobin < 10

g/dL, or use of epoetin, transfusion, or ribavirin dose adjustment, were more frequent (77% vs 63%), more severe (nadir Hgb < 8.5 g/dL in 35% vs 18%), and more likely to be considered a severe adverse event (8% vs 3%) in older patients. The use of epoetin (55% vs 33%) and blood transfusions (23% vs 10%) was also more frequent in the older population. Among treatment naïve patients on telaprevir, rates of on-treatment virological response were similar between older and younger patients [(week 4: 77% (17/22) vs 79% (177/225), respectively]^[41,63].

In conclusion, triple therapy with TVR and BOC is burdened with a number of adverse events, with a higher rate in the older population. However, the rate of discontinuation and of SVR are comparable to those in the younger HCV patients. Undoubtedly, HCV patients until now object of expanded access programs and clinical experience were more prone to develop adverse events, because with a more advanced liver disease.

TOWARDS NEW TREATMENT REGIMENS: IFN-FREE DOESN'T MEAN FREE FROM CONTRAINDICATIONS, SIDE EFFECTS AND INTERACTIONS

At the time this manuscript is written (April 2015), the following new direct antiviral agents (DAAs) or combination of DAAs are approved by the US FDA and the European EMA: sofosbuvir, simeprevir, co-formulated ABT-450/ritonavir/ombitasvir plus dasabuvir, and sofosbuvir plus ledipasvir. Furthermore, one drug is approved only by EMA, *i.e.*, daclatasvir, while the combination of grazoprevir plus elbasvir is currently tested in phase 3 clinical trials. Finally, other combinations of DAAs, *i.e.*, sofosbuvir plus GS-5816 (Gilead Sciences), and asunaprevir plus daclatasvir plus beclabuvir, are proceeding rapidly in their clinical development and others are likely to enter the market only a little bit later. Therefore, new types of IFN-containing regimens have become and will become available but, mainly, the time has come for IFN-free regimens. Free from IFN means free from all the well-known IFN-dependent contraindications and side effects, and the possibility to consider for treatment also the following three categories of patients which had been almost completely excluded from IFN-based regimens: patients with more advanced disease (decompensated cirrhotics); patients with severe cardio-pulmonary or psychiatric comorbidities; elderly patients, *i.e.*, those aged ≥ 65 years. It is easily understood that the latter two categories of patients frequently coincide.

However, it should be clearly kept in mind that IFN-free does not mean free from any side effect and from the possibility of drug-drug interactions. Moreover, the metabolism and way of elimination of each drug

should be carefully evaluated, mainly when planning to treat older patients with multiple comorbidities and polytherapy. Again, the most worrisome aspect is that registrative studies of new drugs almost completely lack data concerning efficacy and, mainly, safety in this more fragile patient population.

Sofosbuvir has been the first among the new anti-HCV drugs to be approved both in US and in Europe. It is a nucleotide prodrug which, in human hepatocytes, is converted to an active uridin-triphosphate form, which acts as an inhibitor of the HCV RNA-polymerase. In the 4 phase 3 registrative trials, only few patients aged ≥ 65 years have been included and, according to the EMA assessment report as adopted by the Committee for Medicinal Products for Human use (CHMP), "there is lack of clinical experience treating patients older than 75 years of age"^[64]. In the POSITRON trial, in which 207 naïve patients with genotype 2-3 HCV infection were treated with sofosbuvir plus RBV, mean age was 52 (21-75) years, and only 15 patients aged ≥ 65 years received sofosbuvir^[65]. At the univariate analysis, neither age ≥ 50 years [OR = 1.37 (0.70-2.68), $P = 0.36$], nor age ≥ 65 years [OR = 0.77 (0.23-2.54), $P = 0.67$], were associated with a reduced probability of SVR^[65,66]. The number of patients aged ≥ 65 years was limited to 9 in the FUSION trial, in which 201 patients with genotype 2-3 HCV infection, nonresponder to previous IFN-based regimens, were treated with sofosbuvir plus RBV for 12 or 16 wk^[65]. Mean age in this trial was 54 years (24-70), and age ≥ 50 years was not associated with a reduced SVR neither in the 12 wk arm [OR = 1.44 (0.55-3.8), $P = 0.46$], nor in the 16 week one [OR = 1.22 (0.44-3.42), $P = 0.71$]^[65]. Age ≥ 65 years was not evaluated with respect to SVR due to the restriction of the sample. In the FISSION trial, where 256 HCV genotype 2-3 naïve patients were treated with sofosbuvir plus RBV and compared to 243 patients receiving PEG-IFN plus RBV, mean age was 48 (19-77) years, only 7 patients were aged ≥ 65 years, and age ≥ 50 years was not associated with reduced SVR at the univariate analysis [OR = 1.40 (0.83-2.37), $P = 0.21$]^[67]. Finally, in the NEUTRINO trial, in which 327 naïve patients with genotype 1, 4, 5 or 6 HCV infection underwent treatment with PEG-IFN plus RBV plus sofosbuvir, mean age was 52 (19-70) years, and only 20 patients were aged ≥ 65 years^[67]. In this trial there was a trend towards a better response in younger patients, with 94.5% of patients aged < 50 years reaching SVR compared to 88% of those aged ≥ 50 years [OR = 0.42 (0.17-1.06), $P = 0.067$].

The bioavailability of sofosbuvir is at least 50%, it is subjected to marked efflux, probably mediated by P-glycoprotein and/or breast cancer resistance protein, and it undergoes extensive first-pass metabolism in the intestine and in the liver, being rapidly hydrolysed to different metabolites^[64]. Most of radioactively-labelled sofosbuvir is excreted in urine, predominantly in the form of its metabolite GS-331007, and severe renal

impairment is therefore associated with a more than 7-fold increase in exposure to GS-331007. Treatment of patients with severe renal impairment or end-stage renal disease is not recommended. While exposure to sofosbuvir and to its metabolite GS-566500 was increased approximately 2-fold in patients with moderate and severe hepatic impairment, there are no specific recommendations in this category of patients. Possible interactions to consider in patients treated with sofosbuvir are those with drugs inducing intestinal P-glycoprotein (Rifampicin, Carbamazepine, Hypericum), which can reduce sofosbuvir plasmatic concentration, and with those inhibiting P-glycoprotein (Cyclosporine), which can significantly increase sofosbuvir levels.

The experience in elderly patients has been very limited also in the phase 3 registrative trials of simeprevir, which is a macrocyclic inhibitor of the HCV-NS3/4A protease. In the QUEST 1 trial, 264 naïve HCV genotype 1 patients were treated with a triple regimen of PEG-IFN plus RBV plus simeprevir and compared to 130 patients receiving placebo instead of simeprevir^[68]. Mean age was 48 (36-54) years and only 7 patients were older than 65 years^[68]. Age was not associated with SVR^[69]. Comparable age distributions were those in the QUEST 2 trial^[70] [46 (18-73) years], in which 257 naïve HCV genotype 1 patients received PEG-IFN plus RBV plus simeprevir and were compared to 134 patients receiving triple therapy including placebo, and in the PROMISE trial [52 (20-70) years], in which 260 HCV genotype 1 previous relapser were retreated in triple therapy with simeprevir and compared to 133 patients receiving placebo^[71]. Also in these 2 trials age was unrelated to SVR. In the EMA assessment report as adopted by the CHMP, it is therefore stated that the number of patients > 65 years treated with simeprevir is too small to draw meaningful conclusions, and no data at all is available for patients over the age of 73 years^[69]. It is also noted that pruritus and anemia were higher in the > 45 and ≤ 65 year age group of patients treated with simeprevir compared to the incidence in younger patients, and that anemia was reported in 8/21 simeprevir-treated patients > 65 years compared to 1/8 of placebo treated ones in the same age group, suggesting a possible age-related effect of SIM on this side effects^[69]. Simeprevir seems to have an impact also on the incidence of pruritus in the age group >65 years, and of dyspnea in patients > 45 years (16% vs 9.1% in placebo), independently from anemia^[69]. However, no dose adjustment is recommended in the elderly population.

Most of simeprevir administered dose is recovered in *faecies*, (approximately 90%), while excretion in urine accounts to only <0.5% in man^[69]. Since renal elimination of simeprevir is negligible, a certain caution is recommended only in patients with severe renal impairment. Similarly no dose adjustment is necessary in patients with mild or moderate hepatic impairment, but no dose recommendation can be made for patients

with severe hepatic impairment (Child Pugh class C). The primary enzyme involved in the biotransformation of simeprevir is cytochrome CYP3A4, and the potential for interaction of simeprevir is high. Co-administration of simeprevir with moderate or strong inhibitors of CYP3A4 (Erythromycin) may significantly increase the plasma level of simeprevir, while co-administration with moderate or strong inducers of CYP3A4 may significantly reduce its plasma concentration, leading to loss of efficacy^[69].

The experience in the elderly population is even poorer with daclatasvir. Daclatasvir is a first in class direct acting antiviral agent, which binds to and inhibits the function of the hepatitis C virus protein NS5A. In the only phase 3 registrative trial, in which daclatasvir was used in combination with PEG-IFN plus RBV in naïve HCV genotype 4 patients, only 3 among the 82 patients treated with daclatasvir were aged ≥ 65 years^[72].

The elimination of daclatasvir in animals involved multiple pathways including fecal excretion, direct intestinal secretion, and metabolism followed by biliary excretion, while renal clearance was a minor route of elimination for daclatasvir^[73]. Therefore, no dose adjustment of daclatasvir is required for patients with any degree of renal impairment. daclatasvir is metabolized by CYP3A4 as well as excreted unchanged by P-glycoprotein and possible other transporters. It is therefore expected that strong inhibitors (*e.g.*, ketoconazole) and inducers (rifampicin) of CYP3A4 and/or P-glycoprotein will influence the exposure to daclatasvir to a significant extent. Since daclatasvir is an inhibitor of P-glycoprotein, organic anion transporting polypeptide (OATP) 1B1 and 1B3, organic cation transporter (OCT)1 and breast cancer resistance protein (BCRP), the exposure to drugs transported by these enzymes (rosuvastatin, digoxin) may be increased by coadministration of daclatasvir^[73].

The combination treatment of co-formulated ABT-450/ritonavir/ombitasvir plus dasabuvir was very recently approved. ABT-450, a HCV NS3/4A protease inhibitor, is administered with ritonavir, which acts as a pharmaco-enhancer, without direct antiviral action, inhibiting ABT-450 metabolism and increasing its blood concentrations. Ombitasvir is a HCV NS5A inhibitor, while dasabuvir is a non-nucleoside NS5B polymerase inhibitor.

In the 6 phase 3 registrative trials (SAPPHIRE-1^[74], PEARL-4 and PEARL-3^[75], SAPPHIRE-2^[76], PEARL-2^[77] and TURQUOISE-2^[78]), the proportion of patients aged more than 65 years was, respectively, of 4.0% (19 patients), 7.5% (23 patients), 7.9% (33 patients), 6.7% (20 patients), 16.7% (31 patients) and 12.9% (49 patients). All trials excluded patients over 70 years of age. Overall, a reduced probability of SVR with age ≥ 55 years was not reported in any of these studies, although age ≥ 65 years was not evaluated with respect to SVR due to the restriction of the sample. Concerning safety, according to the EMA assessment

report as adopted by the CHMP, "within each age group (< 65 years, ≥ 65 years), the treatment-group differences in the incidence of treatment-emergent adverse events and the percentage of subjects with hemoglobin and liver function test values by maximum grade were generally consistent with those observed in the overall analysis"^[79,80].

The bioavailability of ABT-450/ritonavir/ombitasvir and dasabuvir was mainly evaluated in the combination therapy, possibly accounting for interactions between individual DAAs, and only partially in the single agent administration. All these drugs are prevalently transported in plasma as unchanged products (ABT-450 and ombitasvir) or active metabolites (M1 for dasabuvir), metabolized by the CYP3A or CYP2C cytochromes and excreted with the faeces (approximately 87%-94%) through the hepatobiliary route and, in a minor part, with urine^[79,80]. Notwithstanding exposures were shown to be altered in different extents with renal and hepatic impairment, there are no specific recommendations in this categories of patients^[79,80]. As for other treatment regimens, possible interactions to consider are those with drugs inhibiting (ketoconazole, cyclosporine, protease inhibitors) or inducing (carbamazepine) CYP3A4, or inhibiting CYP2C8 and OATP1B (gemfibrozil).

Also the combination of sofosbuvir and ledipasvir, a new HCV NS5A inhibitor with antiviral activity against genotype 1, was recently approved. This regimen, with or without RBV, reached very high SVR rates both in previously untreated patients (ION-1 and ION-3 trials)^[81,82], and in those who had failed a previous triple therapy with boceprevir or telaprevir (ION-2 trial)^[83]. Baseline patient characteristics were similar in these trials except that up to 20% of patients had cirrhosis in ION-1 and ION-2 trials, while the ION-3 trial included only non-cirrhotic patients. As a whole, 1952 patients were enrolled in these phase 3 studies, with a median age of 55 years (range: 18-80 years)^[84], and with only 152 patients aged > 65 years [ION1: 72 patients (8.3%); ION2: 31 patients (4.8%); ION3: 49 patients (7.6%)]^[81-83]. When analyzed at the univariate analysis, age was not associated with a reduced probability of SVR^[83]. Overall, the safety profile of sofosbuvir plus ledipasvir in patients with compensated liver disease and with a calculated GFR > 60 ml/min is very favorable, but caution is recommended both in patients with severe liver disease and in patients with severe renal impairment^[84].

Although the absolute bioavailability of ledipasvir has not been investigated, the fraction absorbed seemed to be modest (< 30%) and mostly excreted *via* biliary secretion^[84]. It is not a substrate of the hepatic transporters but co-administration of ledipasvir has an effect on exposure to sofosbuvir (about 2-fold increase) *via* its inhibitory effects on P-glycoprotein and/or breast cancer resistance protein, for which sofosbuvir is a substrate^[84].

Finally, the combination of grazoprevir plus elbasvir, with or without RBV, is under investigation

in large phase 3 clinical trials. Grazoprevir is a second generation protease inhibitor with potent antiviral efficacy and broad genotypic coverage, while elbasvir is a potent NS5A inhibitor. The safety profile is good and SVR rates are high^[85,86]. Currently extrapolable data concerning the elderly population are poor but subgroup analysis showed that SVR was not influenced by age and was similar between patients older than 50 years and the younger ones^[84,85].

HOW TO REVISE THE STRATEGY OF TREATMENT IN THE ELDERLY IN THE ERA OF IFN-FREE REGIMENS?

As pointed out above, although with some differences between countries, it seems clear that elderly patients are becoming the prevalent HCV-affected population^[7-15]. It has also been acquired that the progression of HCV-related hepatitis towards cirrhosis and HCC is more rapid in the elderly^[27-30], and that aged patients likely suffer more also from the extra-hepatic manifestations of HCV infection, such as fatigue and neuropsychological disorders^[22]. Moreover, notwithstanding the problems associated with IFN treatment in the elderly, the few studies available demonstrate that aged patients can achieve significant rates of SVR and that SVR can halt the progression of liver disease also in this category of patients (Table 1). Our narrowness of mind towards the treatment of HCV in the elderly has been mainly dependent on the fact that, to date, we have had available only IFN-based regimens, which in older patients are burdened with more side effects, higher discontinuation and withdrawal rates, and lower SVR rates, the latter probably due to a reduced stimulatory effect of IFN on the aged immune system. Indeed, although numbers are still limited, the first data from IFN-free regimens suggest that SVR rates are substantially independent from age^[65-68,70,71]. However, it should be kept in mind that, even if to a significantly lesser extent, also new drugs have contraindications, side effects and interactions. Indeed, the main problem of the new anti-HCV regimens in elderly patients will likely be that of combining different anti-viral drugs, each with its potential of interactions, in patients who are frequently on polytherapy due to comorbidities.

In any case, with the transition to IFN-free regimens, it seems fundamental that we change our mind concerning the treatment of HCV infection in the elderly. As well as in the young patient, also in the aged one, we should start with the principle that HCV infection deserves to be eradicated because of the risk of progression towards cirrhosis and HCC and, even independently from liver disease, because of its negative impact on the quality of life. Having said that, there are two possible scenarios to be considered: (1) the ideal one, the more desirable, is that in which there are no economic restrictions; and (2) the other

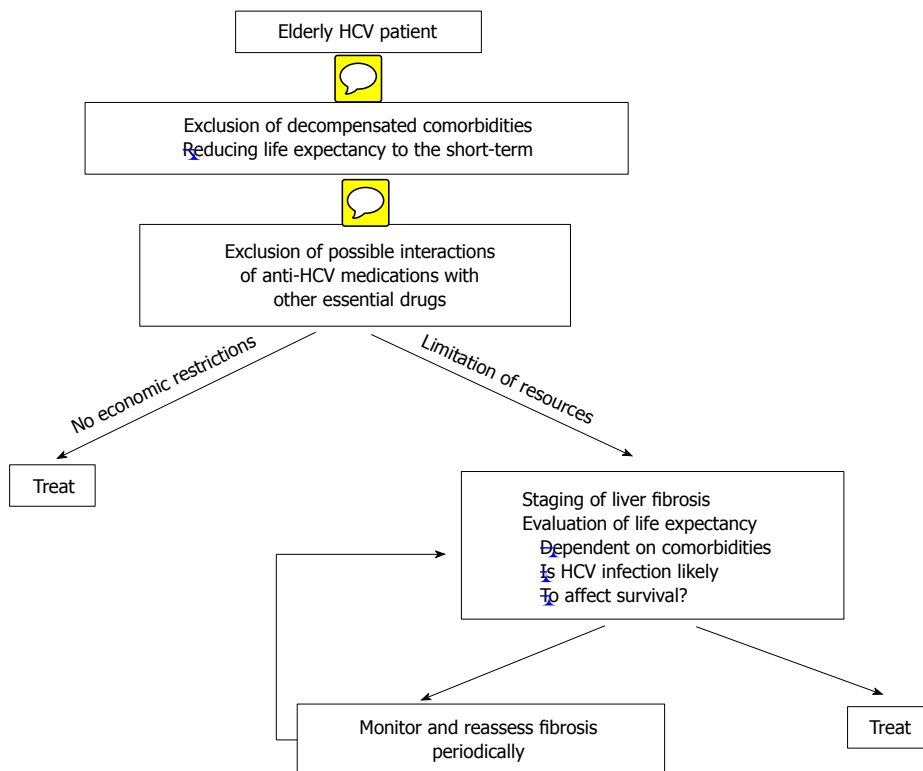


Figure 1 Proposal for the evaluation of possible candidates to interferon-free anti-hepatitis C virus regimens among elderly patients.

one, which will be likely faced by most of the countries, is that in which the resources are limited. If moving in the first scenario, every elderly HCV-positive patient, independently from the stage of liver fibrosis, should be considered a candidate to antiviral treatment, and the only limitations should be decompensated/advanced comorbidities (cardio-pulmonary diseases, cancers, etc.), which are expected to affect short-term survival (in terms of months or, at most, of a very few years), or possible interactions of anti-HCV medications with drugs which are essential for the management of patient comorbidities (Figure 1). In the more realistic second scenario, conversely, after having excluded severe comorbidities likely to affect short-term survival and binding pharmacological interactions, every single case should be carefully evaluated on the base of: (1) the stage of liver fibrosis and expected time to decompensation; and (2) the evaluation of life-expectancy dependent on comorbidities. According to these assessment, independently from anagraphic age, the elderly HCV patients should receive the indication to treatment when liver disease is likely to affect survival. Patients who are not considered for treatment should be monitored and periodically (annually) noninvasively reassessed in terms of fibrosis, with the readiness to reconsider the indication to treatment if the equilibrium seems to have changed (Figure 1).

CONCLUSION

In the present manuscript, an updated overview

concerning the issue of HCV treatment in the elderly patient is provided. As well as it happened in the case HBV infection, the availability of safe and effective drugs will change our approach also to the aged HCV patient, and the number of treatment candidates will rise dramatically in the next future. The sooner we will change our mind with respect to an *a priori* obstacle for anti-HCV treatment in the elderly, the sooner we will begin to spare many aged HCV patients from avoidable liver-related complications.

REFERENCES

- 1 **Armstrong GL**, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000; **31**: 777-782 [PMID: 10706572 DOI: 10.1002/hep.510310332]
- 2 **Global Burden Of Hepatitis C Working Group**. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; **44**: 20-29 [PMID: 14681338 DOI: 10.1177/0091270003258669]
- 3 **Alter MJ**. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441 [PMID: 17552026]
- 4 **Alter MJ**, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999; **341**: 556-562 [PMID: 10451460 DOI: 10.1056/NEJM199908193410802]
- 5 **Armstrong GL**, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705-714 [PMID: 16702586]
- 6 **McHutchison JG**. Understanding hepatitis C. *Am J Manag Care* 2004; **10**: S21-S29 [PMID: 15084064]
- 7 **Dore GJ**, Law M, MacDonald M, Kaldor JM. Epidemiology

- of hepatitis C virus infection in Australia. *J Clin Virol* 2003; **26**: 171-184 [PMID: 12600649 DOI: 10.1016/S1386-6532(02)00116-6]
- 8 **Gérard C**, Delwaide J, Vaira D, Bastens B, Servais B, Wain E, Bataille C, Daenen G, Belaïche J. Evolution over a 10 year period of the epidemiological profile of 1,726 newly diagnosed HCV patients in Belgium. *J Med Virol* 2005; **76**: 503-510 [PMID: 15977247 DOI: 10.1002/jmv.20390]
 - 9 **Payan C**, Roudot-Thoraval F, Marcellin P, Bled N, Duverlie G, Fouchard-Hubert I, Trimoulet P, Couzigou P, Cointe D, Chaput C, Henquell C, Abergel A, Pawlotsky JM, Hezode C, Coudé M, Blanchi A, Alain S, Loustaud-Ratti V, Chevallier P, Trepo C, Gerolami V, Portal I, Halfon P, Bourlière M, Bogard M, Plouvier E, Laffont C, Agius G, Silvain C, Brodard V, Thieffin G, Buffet-Janvresse C, Riachi G, Grattard F, Bourlet T, Stoll-Keller F, Doffoel M, Izopet J, Barange K, Martinot-Peignoux M, Branger M, Rosenberg A, Sogni P, Chaix ML, Pol S, Thibault V, Opolon P, Charrois A, Serfaty L, Fouqueray B, Grange JD, Lefrère JJ, Lunel-Fabiani F. Changing of hepatitis C virus genotype patterns in France at the beginning of the third millennium: The GEMHEP GenoCII Study. *J Viral Hepat* 2005; **12**: 405-413 [PMID: 15985012 DOI: 10.1111/j.1365-2893.2005.00605.x]
 - 10 **Baldo V**, Floreani A, Menegon T, Angiolelli G, Trivello R. Prevalence of antibodies against hepatitis C virus in the elderly: a seroepidemiological study in a nursing home and in an open population. The Collaborative Group. *Gerontology* 2000; **46**: 194-198 [PMID: 10859458]
 - 11 **Guadagnino V**, Stroffolini T, Rapicetta M, Costantino A, Kondili LA, Menniti-Ippolito F, Caroleo B, Costa C, Griffo G, Loiacono L, Pisani V, Focà A, Piazza M. Prevalence, risk factors, and genotype distribution of hepatitis C virus infection in the general population: a community-based survey in southern Italy. *Hepatology* 1997; **26**: 1006-1011 [PMID: 9328327 DOI: 10.1002/hep.510260431]
 - 12 **Stroffolini T**, Menchinelli M, Taliani G, Dambrosio V, Poliandri G, Bozza A, Lecce R, Clementi C, Ippolito FM, Compagnoni A. High prevalence of hepatitis C virus infection in a small central Italian town: lack of evidence of parenteral exposure. *Ital J Gastroenterol* 1995; **27**: 235-238 [PMID: 8541572]
 - 13 **Okayama A**, Stuver SO, Tabor E, Tachibana N, Kohara M, Mueller NE, Tsubouchi H. Incident hepatitis C virus infection in a community-based population in Japan. *J Viral Hepat* 2002; **9**: 43-51 [PMID: 11851902]
 - 14 **Sawabe M**, Arai T, Esaki Y, Fukazawa T, Takubo K. Persistent infection of hepatitis C virus in the elderly: a clinical and quantitative pathological study of autopsy cases. *Liver* 1999; **19**: 335-342 [PMID: 10459633]
 - 15 **Abdel-Aziz F**, Habib M, Mohamed MK, Abdel-Hamid M, Gamil F, Madkour S, Mikhail NN, Thomas D, Fix AD, Strickland GT, Anwar W, Sallam I. Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. *Hepatology* 2000; **32**: 111-115 [PMID: 10869297 DOI: 10.1053/jhep.2000.8438]
 - 16 **Chiaramonte M**, Stroffolini T, Lorenzoni U, Minniti F, Conti S, Floreani A, Ntakirutimana E, Vian A, Ngatchu T, Naccarato R. Risk factors in community-acquired chronic hepatitis C virus infection: a case-control study in Italy. *J Hepatol* 1996; **24**: 129-134 [PMID: 8907564]
 - 17 **Frank C**, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, El Khoby T, Abdel-Wahab Y, Aly Ohn ES, Anwar W, Sallam I. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000; **355**: 887-891 [PMID: 10752705 DOI: 10.1016/S0140-6736(99)06527-7]
 - 18 **Moriya T**, Koyama T, Tanaka J, Mishiro S, Yoshizawa H. Epidemiology of hepatitis C virus in Japan. *Intervirology* 1999; **42**: 153-158 [PMID: 10516469 DOI: 24974]
 - 19 **Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc 2012; **60**: E1-E25 [PMID: 22994865 DOI: 10.1111/j.1532-5415.2012.04188.x]**
 - 20 **Vespasiani-Gentilucci U**, Gallo P, De Vincentis A, Galati G, Picardi A. Hepatitis C virus and metabolic disorder interactions towards liver damage and atherosclerosis. *World J Gastroenterol* 2014; **20**: 2825-2838 [PMID: 24659875 DOI: 10.3748/wjg.v20.i11.2825]
 - 21 **Chong CA**, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, Krahn M. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003; **98**: 630-638 [PMID: 12650799]
 - 22 **Hassoun Z**, Willems B, Deslauriers J, Nguyen BN, Huet PM. Assessment of fatigue in patients with chronic hepatitis C using the Fatigue Impact Scale. *Dig Dis Sci* 2002; **47**: 2674-2681 [PMID: 12498284]
 - 23 **Hsu PC**, Krajden M, Yoshida EM, Anderson FH, Tomlinson GA, Krahn MD. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? *Liver Int* 2009; **29**: 449-458 [PMID: 19267865 DOI: 10.1111/j.1478-3231.2008.01865.x]
 - 24 **Horikawa N**, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *Gen Hosp Psychiatry* 2003; **25**: 34-38 [PMID: 12583926]
 - 25 **Nudo CG**, 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 [PMID: 17001400]
 - 26 **Honda T**, Katano Y, Shimizu J, Ishizu Y, Doizaki M, Hayashi K, Ishigami M, Itoh A, Hirooka Y, Nakano I, Urano F, Yoshioka K, Toyoda H, Kumada T, Goto H. Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. *Liver Int* 2010; **30**: 527-537 [PMID: 19523048 DOI: 10.1111/j.1478-3231.2009.02064.x]
 - 27 **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 [PMID: 11434620]
 - 28 **Pradat P**, Voirin N, Tillmann HL, Chevallier M, Trépo C. Progression to cirrhosis in hepatitis C patients: an age-dependent process. *Liver Int* 2007; **27**: 335-339 [PMID: 17355454 DOI: 10.1111/j.1478-3231.2006.01430.x]
 - 29 **Tong MJ**, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995; **332**: 1463-1466 [PMID: 7739682 DOI: 10.1056/NEJM199506013322202]
 - 30 **Ohishi W**, Kitamoto M, Aikata H, Kamada K, Kawakami Y, Ishihara H, Kamiyasu M, Nakanishi T, Tazuma S, Chayama K. Impact of aging on the development of hepatocellular carcinoma in patients with hepatitis C virus infection in Japan. *Scand J Gastroenterol* 2003; **38**: 894-900 [PMID: 12940445]
 - 31 **Ratziu V**, Dargere D, Conti M. Increased fibrotic response in the ageing liver. *Hepatology* 2000; **32**: 302A
 - 32 **Horiike N**, Masumoto T, Nakanishi K, Michitaka K, Kurose K, Ohkura I, Onji M. Interferon therapy for patients more than 60 years of age with chronic hepatitis C. *J Gastroenterol Hepatol* 1995; **10**: 246-249 [PMID: 7548798]
 - 33 **Arase Y**, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, Hosaka T, Sezaki H, Yatsuji H, Kawamura Y, Kobayashi M, Kumada H. Interferon-induced prolonged biochemical response reduces hepatocarcinogenesis in hepatitis C virus infection. *J Med Virol* 2007; **79**: 1485-1490 [PMID: 17705189 DOI: 10.1002/jmv.20925]
 - 34 **Hsu YC**, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, Wu MS, Liu YY, Wu CY. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology* 2014; **59**: 1293-1302 [PMID: 24122848 DOI: 10.1002/hep.26892]
 - 35 **Ikeda K**, Arase Y, Kawamura Y, Yatsuji H, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Saitoh S, Suzuki F, Suzuki Y, Kumada H. Necessities of interferon therapy in elderly patients with chronic hepatitis C. *Am J Med* 2009; **122**: 479-486 [PMID: 19375558 DOI: 10.1016/j.amjmed.2008.09.045]

- 36 **Lok AS**, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Goodman ZD. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 2009; **136**: 138-148 [PMID: 18848939 DOI: 10.1053/j.gastro.2008.09.014]
- 37 **National Institutes of Health**. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. *Hepatology* 2002; **36**: S3-20 [PMID: 12407572 DOI: 10.1053/jhep.2002.37117]
- 38 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. 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 [PMID: 11583749]
- 39 **Hadziyannis SJ**, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676]
- 40 **Coco B**, Caraceni P, Aghemo A, Bitetto D, Bruno R, Ciancio A, Marzoni M, Petta S, Rendina M, Valenti L. Triple therapy with first-generation protease inhibitors for patients with genotype 1 chronic hepatitis C: recommendations of the Italian association for the study of the liver (AISF). *Dig Liver Dis* 2014; **46**: 18-24 [PMID: 24119482 DOI: 10.1016/j.dld.2013.08.243]
- 41 **Gordon SC**, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, Maliakkal B, Alam I, Stewart TG, Vainorius M, Peter J, Nelson DR, Fried MW, Reddy KR. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. *J Hepatol* 2015; **62**: 286-293 [PMID: 25218788 DOI: 10.1016/j.jhep.2014.08.052]
- 42 **Antonucci G**, Longo MA, Angeletti C, Vairo F, Oliva A, Comandini UV, Tocci G, Boumis E, Noto P, Solmone MC, Capobianchi MR, Girardi E. 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; **102**: 1383-1391 [PMID: 17403072 DOI: 10.1111/j.1572-0241.2007.01201.x]
- 43 **Thabut D**, Le Calvez S, Thibault V, Massard J, Munteanu M, Di Martino V, Ratziu V, Poynard T. Hepatitis C in 6,865 patients 65 yr or older: a severe and neglected curable disease? *Am J Gastroenterol* 2006; **101**: 1260-1267 [PMID: 16771947 DOI: 10.1111/j.1572-0241.2006.00556.x]
- 44 **Frei P**, Leucht AK, Held U, Kofmehl R, Manser CN, Schmitt J, Mertens J, Rau M, Baur K, Gerlach T, Negro F, Heim M, Moradpour D, Cerny A, Dufour JF, Müllhaupt B, Geier A. Elderly age is not a negative predictive factor for virological response to therapy with pegylated interferon- α and ribavirin in chronic hepatitis C virus patients. *Liver Int* 2014; **34**: 551-557 [PMID: 24034338 DOI: 10.1111/liv.12279]
- 45 **Dalgard O**, Bjørø K, Hellum KB, Myrvang B, Ritland S, Skaug K, Raknerud N, Bell H. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology* 2004; **40**: 1260-1265 [PMID: 15558712 DOI: 10.1002/hep.20467]
- 46 **von Wagner M**, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Häussinger D, Herrmann E, Zeuzem S. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; **129**: 522-527 [PMID: 16083709 DOI: 10.1016/j.gastro.2005.05.008]
- 47 **Mangia A**, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annesse M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609-2617 [PMID: 15972867 DOI: 10.1056/NEJMoa042608]
- 48 **Kainuma M**, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Satoh T, Maruyama T, Nakamura M, Kotoh K, Azuma K, Shimono J, Shimoda S, Hayashi J. Pegylated interferon α -2b plus ribavirin for older patients with chronic hepatitis C. *World J Gastroenterol* 2010; **16**: 4400-4409 [PMID: 20845506]
- 49 **Zhou H**, Luo H, Xiao S, Wang H, Gong G. Predictors for dose reduction of antiviral therapy in older patients infected with hepatitis C virus: a meta-regression analysis. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 491-498 [PMID: 24193376 DOI: 10.1007/s10096-013-1992-8]
- 50 **Iwasaki Y**, Ikeda H, Araki Y, Osawa T, Kita K, Ando M, Shimoe T, Takaguchi K, Hashimoto N, Kobatake T, Tomita M, Kawaguchi M, Kobashi H, Sakaguchi K, Shiratori Y. Limitation of combination therapy of interferon and ribavirin for older patients with chronic hepatitis C. *Hepatology* 2006; **43**: 54-63 [PMID: 16374855 DOI: 10.1002/hep.20984]
- 51 **Yang Z**, Zhuang L, Yang L, Liu C, Lu Y, Xu Q, Chen X, Chen L. Efficacy and safety of peginterferon plus ribavirin for patients aged \geq 65 years with chronic hepatitis C: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2014; **38**: 440-450 [PMID: 24176812 DOI: 10.1016/j.clinre.2013.08.013]
- 52 **Hézode C**, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360**: 1839-1850 [PMID: 19403903 DOI: 10.1056/NEJMoa0807650]
- 53 **McHutchison JG**, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; **362**: 1292-1303 [PMID: 20375406 DOI: 10.1056/NEJMoa0908014]
- 54 **Kwo PY**, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, Davis MN, Galati JS, Gordon SC, Ravendhran N, Rossaro L, Anderson FH, Jacobson IM, Rubin R, Koury K, Pedicone LD, Brass CA, Chaudhri E, Albrecht JK. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon α -2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; **376**: 705-716 [PMID: 20692693 DOI: 10.1016/S0140-6736(10)60934-8]
- 55 **Poordad F**, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]
- 56 **Bacon BR**, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]
- 57 **Hézode C**, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol* 2013; **59**: 434-441 [PMID: 23669289 DOI: 10.1016/j.jhep.2013.04.035]
- 58 **Colombo M**, Fernández I, Abdurakhmanov D, Ferreira PA, Strasser SI, Urbanek P, Moreno C, Streinu-Cercel A, Verheyen A, Iraqui W, DeMasi R, Hill A, Läufler JM, Lonjon-Domanec I, Wedemeyer H. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. *Gut* 2014; **63**: 1150-1158 [PMID: 24201995 DOI: 10.1136/

- gutjnl-2013-305667]
- 59 **Hézode C**, Fontaine H, Dufour C, Larrey DG, Zoulim F, De Ledinghen V, Canva-Delcambre V, Alric L, Bourliere M, Pol S, Poynard T, Riachi G, Bernard PH, Raabe JJ, Gournay J, Pawlowsky JM, Metivier S, Samuel D, Barthe, Carrat F, Bronowicki JP. Efficacy and safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in cirrhotics according to the age. Data from the CUPIC cohort (ANRS CO20). *Hepatology* 2013; 58 Suppl 1: 1092A-1093A [DOI: 10.1002/hep.26880]
 - 60 **Moreno C**, Wedemeyer H, Fernandez I, Abrao Ferreira P, Strasser SI, Urbanek P, Abdurakhmanov D, Streinu-Cercel A, Gaeta GB, Beelden F, Iraqui W, De Masi R, Hill A, Lauffer JM, Lonjon-Domanec I, Colombo M. Efficacy and safety results of treatment of patients over 65 years old with genotype 1 hepatitis C with severe fibrosis or compensated cirrhosis: the International Telaprevir Early Access Program. *Hepatology* 2013; 58 Suppl 1: 1130A-1131A
 - 61 **Karino T**, Ozeki I, Hige S, Kimura M, Arakawa T, Nakajima T, Kuwata Y, Sato T, Ohmura T, Toyota J. Telaprevir impairs renal function and increases blood ribavirin concentration during telaprevir/pegylated interferon/ribavirin therapy for chronic hepatitis C. *J Viral Hepat* 2014; 21: 341-347 [PMID: 24001168 DOI: 10.1111/jvh.12162]
 - 62 **Rao S**, Kontorinis N, Tarquinio L, Kong J, Mollison L, Mac Quillan G, Adams L, Jeffrey G, Galhenage S, Nazareth S, Totten L, Vallve J, Cheng W. Direct acting antiviral drugs in chronic hepatitis C and renal toxicity. *Hepatol Int* 2014; 8 Suppl 1: S167
 - 63 **Aronsohn A**, Stainbrook T, Mohanty S, Mubarak A, Spivey J, Pandya P, Steward T, Fried MW, Jacobson IM. Impact of age on safety and treatment response in patients with hepatitis C treated with Boceprevir or Telaprevir. *Hepatology* 58 Suppl 1: 218A
 - 64 **European Medicines Agency**. Sovaldi: EPAR-Public assessment report. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002798/WC500160600.pdf
 - 65 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; 368: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]
 - 66 **Mangia A**. Virologic Response Rates to Sofosbuvir-Containing Regimens Are Similar in Patients With and Without Traditional Negative Predictive Factors: a Retrospective Analysis of Phase 3 Data. Annual Meeting of the American Association of Study of Liver Disease, 2013
 - 67 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 368: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]
 - 68 **Jacobson IM**, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O, Ouwkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; 384: 403-413 [PMID: 24907225 DOI: 10.1016/S0140-6736(14)60494-3]
 - 69 **European Medicines Agency**. Olysio: EPAR-Public assessment report. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002777/WC500167870.pdf
 - 70 **Manns M**, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M, Lenz O, Ouwkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; 384: 414-426 [PMID: 24907224 DOI: 10.1016/S0140-6736(14)60538-9]
 - 71 **Forns X**, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O, Ouwkerk-Mahadevan S, Scott J, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; 146: 1669-79.e3 [PMID: 24602923 DOI: 10.1053/j.gastro.2014.02.051]
 - 72 **Hézode C**, Hirschfield GM, Ghesquiere W, Sievert W, Rodriguez-Torres M, Shafran SD, Thuluvath PJ, Tatum HA, Waked I, Esmat G, Lawitz EJ, Rustgi VK, Pol S, Weis N, Pockros PJ, Bourliere M, Serfaty L, Vierling JM, Fried MW, Weiland O, Brunetto MR, Everson GT, Zeuzem S, Kwo PY, Sulkowski M, Bräu N, Hernandez D, McPhee F, Wind-Rotolo M, Liu Z, Noviello S, Hughes EA, Yin PD, Schnittman S. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut* 2015; 64: 948-956 [PMID: 25080450 DOI: 10.1136/gutjnl-2014-307498]
 - 73 **European Medicines Agency**. Daklinza: EPAR-Public assessment report. Available from: URL: http://www.google.it/url?url=http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003768/WC500172849.pdf&rct=j&frm=1&q=&esrc=s&sa=U&ei=U6mmVMXfD8u2UabXg7AL&ved=0CC4QFjAE&usq=AFQjCNFA DK9Q-zWKmO4jIGx1Nr7vNSZfXQ
 - 74 **Feld JJ**, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370: 1594-1603 [PMID: 24720703 DOI: 10.1056/NEJMoa1315722]
 - 75 **Ferenci P**, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; 370: 1983-1992 [PMID: 24795200 DOI: 10.1056/NEJMoa1402338]
 - 76 **Zeuzem S**, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370: 1604-1614 [PMID: 24720679 DOI: 10.1056/NEJMoa1401561]
 - 77 **Andreone P**, Colombo MG, Enejosa JV, Koksai I, Ferenci P, Maieron A, Müllhaupt B, Horsmans Y, Weiland O, Reesink HW, Rodrigues L, Hu YB, Podsadecki T, Bernstein B. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014; 147: 359-365.e1 [PMID: 24818763 DOI: 10.1053/j.gastro.2014.04.045]
 - 78 **Poordad F**, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Forns X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; 370: 1973-1982 [PMID: 24725237 DOI: 10.1056/NEJMoa1402869]
 - 79 **European Medicines Agency**. Viekirax: EPAR-Public assessment report. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003839/WC500183999.pdf

- 80 **European Medicines Agency**. Exviera: EPAR-Public assessment report. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003837/WC500182235.pdf
- 81 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]
- 82 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]
- 83 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI: 10.1056/NEJMoa1316366]
- 84 **European Medicines Agency**. Harvoni: EPAR-Public assessment report. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003850/WC500177996.pdf
- 85 **Lawitz E**, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, Alric L, Bronowicki JP, Lester L, Sievert W, Ghalib R, Balart L, Sund F, Lagging M, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1075-1086 [PMID: 25467591 DOI: 10.1016/S0140-6736(14)61795-5]
- 86 **Sulkowski M**, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, Kugelmas M, Murillo A, Weis N, Nahass R, Shibolet O, Serfaty L, Bourliere M, DeJesus E, Zuckerman E, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1087-1097 [PMID: 25467560 DOI: 10.1016/S0140-6736(14)61793-1]
- 87 **Bresci G**, Del Corso L, Romanelli AM, Giuliano G, Pentimone F. The use of recombinant interferon alfa-2b in elderly patients with anti-HCV-positive chronic active hepatitis. *J Am Geriatr Soc* 1993; **41**: 857-862 [PMID: 7688007]
- 88 **Van Thiel DH**, Friedlander L, Caraceni P, Molloy PJ, Kania RJ. Treatment of hepatitis C virus in elderly persons with interferon alpha. *J Gerontol A Biol Sci Med Sci* 1995; **50**: M330-M333 [PMID: 7583805]
- 89 **Alessi N**, Freni MA, Spadaro A, Ajello A, Turiano S, Migliorato D, Ferrau O. Efficacy of interferon treatment (IFN) in elderly patients with chronic hepatitis C. *Infez Med* 2003; **11**: 208-212 [PMID: 14988669]
- 90 **Imai Y**, Kasahara A, Tanaka H, Okanoue T, Hiramatsu N, Tsubouchi H, Yoshioka K, Kawata S, Tanaka E, Hino K, Hayashi K, Tamura S, Itoh Y, Sasaki Y, Kiyosawa K, Kakumu S, Okita K, Hayashi N. Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. *J Gastroenterol* 2004; **39**: 1069-1077 [PMID: 15580400 DOI: 10.1007/s00535-004-1448-0]
- 91 **Koyama R**, Arase Y, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, Akuta N, Someya T, Hosaka T, Sezaki H, Kobayashi M, Kumada H. Efficacy of interferon therapy in elderly patients with chronic hepatitis C. *Intervirolgy* 2006; **49**: 121-126 [PMID: 16428887 DOI: 10.1159/000089372]
- 92 **Honda T**, Katano Y, Urano F, Murayama M, Hayashi K, Ishigami M, Nakano I, Yoshioka K, Toyoda H, Kumada T, Goto H. Efficacy of ribavirin plus interferon-alpha in patients aged >=60 years with chronic hepatitis C. *J Gastroenterol Hepatol* 2007; **22**: 989-995 [PMID: 17608843 DOI: 10.1111/j.1440-1746.2006.04773.x]
- 93 **Arase Y**, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, Akuta N, Someya T, Koyama R, Hosaka T, Sezaki H, Kobayashi M, Kumada H. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. *Intervirolgy* 2007; **50**: 16-23 [PMID: 17164553 DOI: 10.1159/000096308]
- 94 **Tsui JI**, Currie S, Shen H, Bini EJ, Brau N, Wright TL. Treatment eligibility and outcomes in elderly patients with chronic hepatitis C: results from the VA HCV-001 Study. *Dig Dis Sci* 2008; **53**: 809-814 [PMID: 17823868 DOI: 10.1007/s10620-007-9926-x]
- 95 **Arase Y**, Kawamura Y, Suzuki Y, Suzuki F, Akuta N, Matsumoto N, Seko Y, Sezaki H, Kobayashi M, Hosaka T, Hirakawa M, Saito S, Ikeda K, Kobayashi M, Kumada H. Efficacy of reduction therapy of natural human beta-interferon and ribavirin in elderly patients with chronic hepatitis C, genotype 1b and high viral load. *Hepatol Res* 2012; **42**: 949-957 [PMID: 22612669 DOI: 10.1111/j.1872-034X.2012.01008.x]
- 96 **Zeuzem S**, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, Sarrazin C, Harvey J, Brass C, Albrecht J. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004; **40**: 993-999 [PMID: 15158341 DOI: 10.1016/j.jhep.2004.02.007]
- 97 **Floreani A**, Minola E, Carderi I, Ferrara F, Rizzotto ER, 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 [PMID: 16551333 DOI: 10.1111/j.1532-5415.2006.00643_4.x]
- 98 **Gramenzi A**, Conti F, Felling F, Cursaro C, Riili A, Salerno M, Gitto S, Micco L, Scuteri A, Andreone P, Bernardi M. Hepatitis C Virus-related chronic liver disease in elderly patients: an Italian cross-sectional study. *J Viral Hepat* 2010; **17**: 360-366 [PMID: 19758274 DOI: 10.1111/j.1365-2893.2009.01189.x]
- 99 **Huang CF**, Yang JF, Dai CY, Huang JF, Hou NJ, Hsieh MY, Lin ZY, Chen SC, Hsieh MY, Wang LY, Chang WY, Chuang WL, Yu ML. Efficacy and safety of pegylated interferon combined with ribavirin for the treatment of older patients with chronic hepatitis C. *J Infect Dis* 2010; **201**: 751-759 [PMID: 20102281 DOI: 10.1086/650470]
- 100 **Oze T**, Hiramatsu N, Yakushijin T, Mochizuki K, Oshita M, Hagiwara H, Mita E, Ito T, Fukui H, Inui Y, Hijioka T, Inada M, Kaytayama K, Tamura S, Yoshihara H, Inoue A, Imai Y, Kato M, Miyagi T, Yoshida Y, Tatsumi T, Kiso S, Kanto T, Kasahara A, Takehara T, Hayashi N. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy. *J Hepatol* 2011; **54**: 604-611 [PMID: 21145907 DOI: 10.1016/j.jhep.2010.07.043]
- 101 **Ebinuma H**, Saito H, Tada S, Nakamoto N, Ohishi T, Tsunematsu S, Kumagai N, Tsuchimoto K, Tsukada N, Inagaki Y, Horie Y, Takahashi M, Atsukawa K, Okamura Y, Kanai T, Hibi T. Disadvantages of peginterferon and ribavirin treatment in older patients with chronic hepatitis C: an analysis using the propensity score. *Hepatol Int* 2011; Epub ahead of print [PMID: 22020828 DOI: 10.1007/s12072-011-9312-9]
- 102 **Gramenzi A**, Conti F, Cammà C, Grieco A, Picciotto A, Furlan C, Romagnò D, Costa P, Rendina M, Ancarani F, Chiaramonte M, Verucchi G, Craxi A, Bernardi M, Andreone P. Hepatitis C in the elderly: a multicentre cross-sectional study by the Italian Association for the Study of the Liver. *Dig Liver Dis* 2012; **44**:

674-680 [PMID: 22538206 DOI: 10.1016/j.dld.2012.03.009]

- 103 **Kim HI**, Kim IH, Jeon BJ, Lee S, Kim SH, Kim SW, Lee SO, Lee ST, Kim DG. Treatment Response and Tolerability of Pegylated Interferon- α Plus Ribavirin Combination Therapy in elderly Patients (≥ 65 years) With Chronic Hepatitis C in Korea. *Hepat Mon* 2012; **12**: 430-436 [PMID: 23008722 DOI: 10.5812/

hepatmon.6170]

- 104 **Hu CC**, Lin CL, Kuo YL, Chien CH, Chen SW, Yen CL, Lin CY, Chien RN. Efficacy and safety of ribavirin plus pegylated interferon alfa in geriatric patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2013; **37**: 81-90 [PMID: 23121150 DOI: 10.1111/apt.12112]

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