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Treatment of chronic hepatitis C in elderly patients with chronic kidney disease: a structured review

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Abstract

Hepatitis C (HC) is a public health problem worldwide and has especially high prevalence in patients over 50 years of age. This population is more prone to suffer from chronic kidney disease (CKD) due to HC infections as well as to age and multiple comorbidities. Those with CKD stages 4 or 5 constitute a population of greater pharmacotherapeutic complexity due to pharmacological variability and limited information on the safety and efficacy of the new antivirals for this group of patients. **Objective:** This article systematizes information about medications and proper dosages for treating chronic HC and is based on studies and reports that include elderly patients with CKD. **Materials and method:** This is a structured review of studies carried out in humans with access to full text published between 01/08/2012 and 01/08/2017 in English or Spanish found in PubMed/Medline using the terms: "Hepatitis C", "Aged", and "Renal Insufficiency". **Results**: Eighty-three articles were identified, fourteen of which were selected. In addition, four manuscripts referenced in those publications were included. A table with antiviral dosing information for treatment of HC in elderly patients with CKD was structured. **Discussion:** We present information on adjustment of dosages of antiviral drugs used for chronic HC in elderly patients and CKD. This could favor prescription and monitoring thereby contributing to the effectiveness and safety of these drugs in this population.

Keywords

Hepatitis C, elderly, kidney diseases, antivirals.

INTRODUCTION

Hepatitis C (HC) is an infectious disease caused by the hepatitis C virus (HCV). It is considered a public health problem by the World Health Organization (WHO) because it affects 2% to 3% of the world's population and is associated with high morbidity and mortality rates. Seventy to ninety percent of infected patients progress to chronic liver diseases such as cirrhosis and hepatocellular carcinoma (HCC) and these diseases are sometimes associated with liver transplantation. (1, 2) HC affects vulnerable and largely unattended populations such as users of injected drugs and people with inadequate healthcare.

Chronic HC is also associated with extrahepatic manifestations including dermatological, rheumatologic, hematological and renal disorders. (3) The latter may manifest with proteinuria, a decreased glomerular filtration rate (GFR), or even chronic kidney disease (CKD). (3-8) The development of CKD due to HCV may be related to the development of glomerulonephritis mediated by the accumulation of cryoglobulins, immune complexes of antibodies against HCV, or by deposition of amyloid. (3, 5, 9, 10)

Patients on hemodialysis (HD) are at greater risk of acquiring HCV infections due to repeated exposure to bloodborne pathogens, the need for transfusions, the duration of dialysis, the need for intravenous access and the

manipulation of the catheter. (11, 12) The result is high prevalence of HCV infection in patients with terminal CKD. (12-17) This prevalence is 53% in Colombia. (18)

Worldwide, the prevalence of HC is higher in patients over 50 years of age, (19) and, the highest proportion of cases reported in Colombia is found among patients with 65 years old and over. (20) This population is more prone to hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease and obesity which constitute additional risk factors for the development of CKD. (5, 21, 22) Similarly, typical physiological alterations of age, especially of those organs responsible for metabolism and drug excretion, (23) provoke pharmacological variability which makes this population even more vulnerable to adverse drug events (ADE). (24) Consequently, elderly patients with CKD and chronic HC constitute a population with great pharmacotherapeutic complexity. Furthermore, treatment options for HC in patients with stage 4 or 5 CKD are limited due to poor tolerance and low effectiveness of conventional therapies with interferon (IFN) and ribavirin (RBV). (13, 17, 25). In addition, there is limited information on the safety and efficacy of current direct-acting antiviral (ADA) regimens given that they have not been adequately evaluated in patients with CKD during clinical trials. (12, 26)

For these reasons, information on the dosage, effectiveness and safety of antivirals for treating HC in elderly patients with CKD is needed in order to achieve the best possible health outcomes and avoid ADE. Consequently, the objective of this review was to systematize the medication dosage information for chronic HC from studies or reports that included elderly patients with CKD.

MATERIALS AND METHODS

We searched PubMed/Medline for the following terms: "Hepatitis C" [Mesh] AND "Aged" [Mesh] AND "Renal Insufficiency" [Mesh] filtered for studies conducted in humans published between August 1, 2012 and August 1, 2017 in English or Spanish with access to full text. Studies and report whose samples included elderly patients with CKD and HC were included. Articles were excluded if they did not mention pharmacological management of HC in patients with CKD, articles with incomplete dosage information and articles related to drugs withdrawn by the Food and Drug Administration (FDA), the European Medicines Agency (EMA) or the National Institute of Drug and Food Surveillance of Colombia (INVIMA - Instituto Nacional de Vigilancia de Medicamentos y Alimentos). The search was complemented with publications considered relevant that were referenced in the articles found.

The titles and abstracts of all the articles identified were reviewed by both authors, and decisions to include or exclude articles were made by consensus.

The following information was structured in a database: medication evaluated, HCV genotype, GFR of the patient (s) studied, stage of CKD, dosage used, information on elimination of dialysis, efficacy/effectiveness, ADE, type of study and reference. Efficacy/effectiveness was reported as sustained viral response and defined as undetectable viral load at 12 or 24 weeks after the end of treatment (sustained virological response, SVR12 or SVR24).

The results obtained were compared with dosages for patients with normal renal functioning (Table 1) and with dosage adjustment recommendations presented in UpToDate® and Micromedex®, two databases frequently used by physicians and pharmacists for posology.

RESULTS

We identified 83 articles of which 14 were included. In addition, four articles referenced in the reviewed publications were considered relevant (Figure 1).

Observational analytical studies accounted for 38.9% of the articles, descriptive observational studies accounted for 33.3% and experimental studies accounted for 27.8%.

Information was identified for seven therapeutic strategies using second generation direct-acting antivirals (DAAs) including elbasvir/grazoprevir, paritaprevir/ombitasvir/ritonavir, dasabuvir, sofosbuvir, simeprevir, daclatasvir and asunaprevir combined with PEG-IFN and/or RBV. The studies and reports reviewed contained information on the use of anti-HCV medications for patients between 18 and 79 years of age.

Table 2 shows a summary of the dosage recommendations according to renal function from UpToDate® and Micromedex®) and from the articles and information reviewed for this article. Table 3 presents complete information obtained from our review.

Table 1. Dosages of drugs for treating chronic HCV in patients with normal renal function

Medication	Dose
Elbasvir/grazoprevir	50/100 mg every 24 hours
Ombitasvir/paritaprevir/ritonavir	25/150/100 mg every 24 hours
Dasabuvir	250 mg every 12 hours
Sofosbuvir	400 mg every 24 hours
Simeprevir	150 mg every 24 hours
Ledipasvir/sofosbuvir	90/400 mg every 24 hours
Daclatasvir	60 mg every 24 hours
Asunaprevir	100 mg every 12 hours
RBV	Combined with PEG-IFN α2b according to weight: 800-1400 mg each day in divided doses
	Combined with IFN α2b according to weight: <75 kg: 1000 mg every day or ≥75 kg: 1200 mg every day, administered in divided doses
PEG-IFN α2a	180 µg once a week
PEG-IFN α2b	50-150 µg once a week (1.5 µg/kg/week)

Information extracted from medication package inserts. PEG-IFN: pegylated interferon.

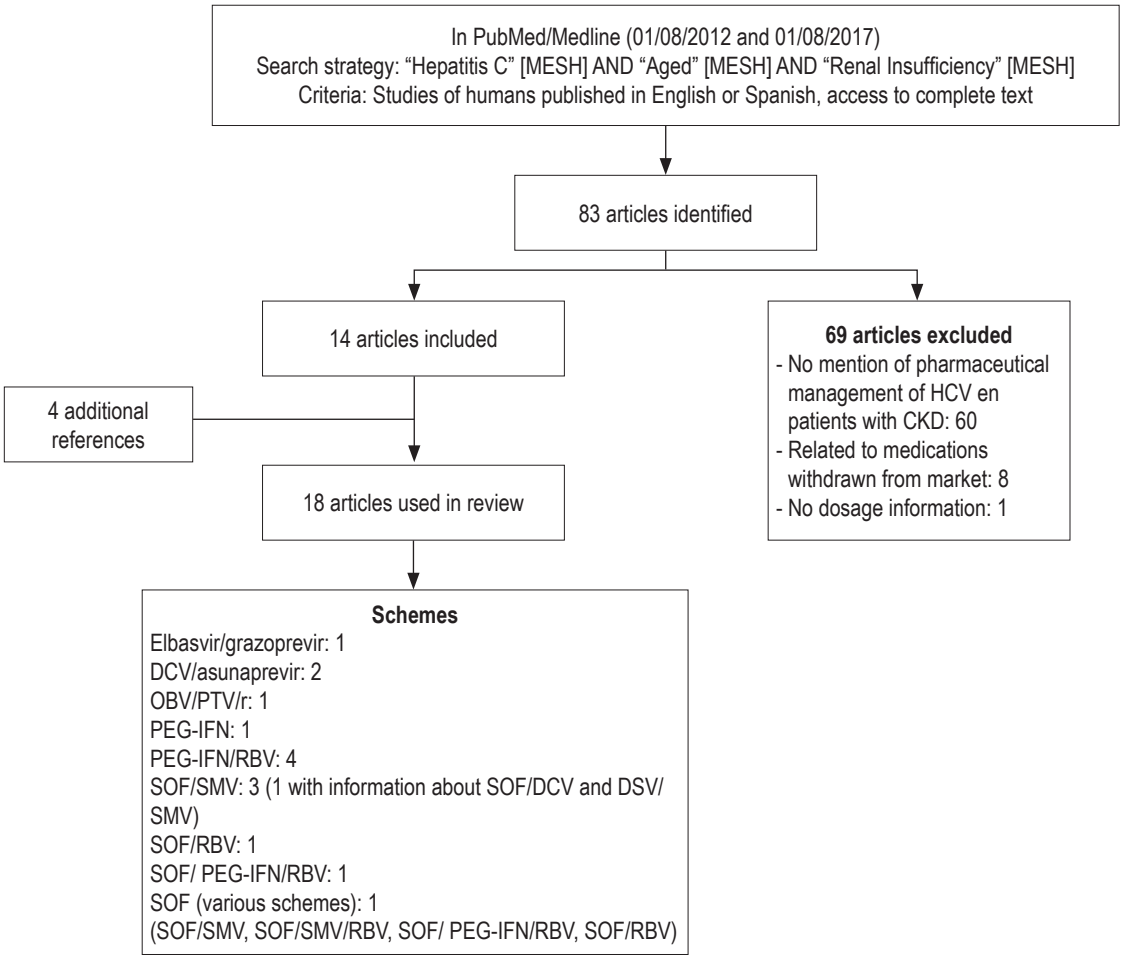

Figure 1. General flowchart of review. DCV: daclatasvir; OBV: ombitasvir; PTV: paritaprevir; r: ritonavir; SMV: simeprevir; SOF: sofosbuvir.

Table 2. Recommendations for adjustment of drug doses for patients with HCV and CKD

Medication	GNT	GFR	Recommendations		
			Uptodate (31)	Micromedex (32)	This review
Elbasvir/ grazoprevir	1a, 1b, 4	>50 mL/min	No dose adjustment necessary	No dose adjustment necessary	50/100 mg every 24 hours (No dose adjustment necessary) (29)
		≤50 mL/ min, TCKD including HD	No dose adjustment necessary, not contraindicated by HD.	No dose adjustment necessary	50/100 mg every 24 hours (No dose adjustment necessary) (29)
Ombitasvir/ paritaprevir/ ritonavir	4	≥15 mL/min	No dose adjustment necessary	No dose adjustment necessary	25/150/100 mg every 24 hours (No dose adjustment necessary) (37-39)
		Dialysis	No dose adjustments are provided on the manufacturer's label (it has not been studied).	No dose adjustment necessary	HD: 25/150/100 mg every 24 hours (No dose adjustment necessary). HD elimination data is limited but suggest that these medications are not extracted by HD. They can be administered at any time - before or after – HD. (39) PS: Doses of 12.5/75/50 mg every 24 hours have been used. Elimination by PD is slower than that observed with conventional HD. Due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD (26)
Dasabuvir	1a, 1b	≥15 mL/min	No dose adjustment necessary	No dose adjustment necessary	250 mg every 12 hours (No dose adjustment necessary) (37, 39)
		Dialysis	No dose adjustments are provided on the manufacturer's label (it has not been studied).	No data	HD: 250 mg every 12 hours (No dose adjustment necessary). HD elimination data is limited but they suggest that these medications are not eliminated by HD. They can be administered at any time - before or after – HD. (39) PD: 250 mg every 12 hours (No dose adjustment necessary). PD: Doses of 12.5/75/50 mg every 24 hours have been used. Elimination by PD is slower than that observed with conventional HD. Due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD. (26)
Sofosbuvir	1a, 1b, 2, 3, 4	≥30 mL/min	No dose adjustment necessary	No dose adjustment necessary	400 mg every 24 hours (No dose adjustment necessary) (35)
		<30 mL/min and TCKD including HD	No dose adjustments are provided on the manufacturer's label (it has not been studied). When renal function is impaired, the predominant metabolites accumulate.	No data	15-29 mL/min/1,73 m^2: 400 mg every 24 hours (No dose adjustment necessary) (27, 33, 35, 40) <15 mL/min/1,73 m^2: 400 mg every 24 hours (No dose adjustment necessary) (9, 27, 33, 35, 40) HD: 400 mg every 24 hours (No dose adjustment necessary) (9, 27, 33, 35, 36) PD: 400 mg every 24 hours (No dose adjustment necessary) (9, 36).
Simeprevir	1	>30 mL/min	No dose adjustment necessary	No dose adjustment necessary	No data
		≤30 mL/ min, TCKD including HD	No dose adjustments are provided on the manufacturer's label (it has not been studied). Dialysis is unlikely to eliminate significant amounts of simeprevir.	Neither the safety nor the efficacy of these drugs have been established in patients with HCV infections and severe CKD.	15-29 mL/min/1,73 m^2: 150 mg every 24 hours (No dose adjustment necessary) (27, 33) <15 mL/min/1,73 m^2: 150 mg every 24 hours (No dose adjustment necessary) (27, 36) HD: 150 mg every 24 hours (No dose adjustment necessary) (27, 33, 36). No information available regarding elimination by HD. They can be administered at any time - before or after – HD. (27) PD: 150 mg every 24 hours (No dose adjustment necessary) (36). No information available regarding elimination by PD.

Table 2. Recommendations for adjustment of drug doses for patients with HCV and CKD. *Continued*

Medication	GNT	GFR	Recommendations		
			Uptodate (31)	Micromedex (32)	This review
Ledipasvir/ sofosbuvir	1, 4, 5, 6	≥30 mL/min	No dose adjustment necessary	No dose adjustment necessary	No information was found on ledipasvir. See sofosbuvir information.
		<30 mL/min	No dose adjustments are provided on the manufacturer's label. However, sofosbuvir and the metabolite accumulate in patients with severe renal insufficiency.	Safety and efficacy have not been established.	
		TCKD including HD intermittent	No dose adjustments are provided on the manufacturer's label. However, sofosbuvir and the metabolite accumulate in patients with severe renal insufficiency. In a 4-hour dialysis session, 18% of the sofosbuvir dose was eliminated.	No data	
Daclatasvir	1,3 *off-label*: 2	Not specified	No dose adjustment necessary	No dose adjustment necessary	HD: 60 mg every 24 hours (No dose adjustment necessary) (13, 16).
Asunaprevir	1, 4	≥30 mL/min	No dose adjustment necessary.	No data	No data
		<30 mL/min	100 mg every 24 hours	No data	No data
		HD	100 mg every 12 hours (it is removed by HD).	No data	HD: 100 mg every 12 hours (No dose adjustment necessary) (13, 16).
RBV	NR	≥50 mL/min	No dose adjustment necessary. necessary (Rebetol capsules/solution, Ribasphere capsules and tablets, Copegus and Moderiba tablet).	No dose adjustment necessary	No data
		<50 mL/min	Use Contraindicated. Children with Cr> 2 mg/dL: permanently discontinue treatment (Rebetol capsules/solution, Ribasphere capsules). Use of Ribasphere tablets not recommended.	Use not recommended. Children with Cr> 2 mg/ dL discontinue treatment (Rebetol)	See recommendations for GFR 30-50 mL/min and <30 mL/min, TCKD including HD.
		30 a 50 mL/ min	Alternate 200 mg and 400 mg every other day (Copegus and Moderiba tablet).	Alternate 200 mg and 400 mg every other day (Copegus).	Alternate 200 and 400 mg daily (41).

Table 2. Recommendations for adjustment of drug doses for patients with HCV and CKD. *Continued*

Medication	GNT	GFR	Recommendations		
			Uptodate (31)	Micromedex (32)	This review
RBV	NR	<30 mL/min, TCKD including HD	200 mg once a day (Copegus y Moderiba tablet)	200 mg once a day (Copegus)	15-29 mL/min/1.73 m^2: 200 mg every 24 hours (33, 39-41) <15 mL/min/1,73 m^2: 200 mg every 24 hours (33, 39-41) HD: 200 mg every 24 hours (39, 41); 200-400 mg weekly (34); 200 mg every 48 hours on days without dialysis (28). Minimal elimination by HD. They can be administered at any time - before or after – HD. (39). Due to the large volume of distribution, RBV is not efficiently eliminated by HD because only a small part of the total amount of drug in the body is available to be eliminated by HD. (41) PD: 200 mg every 24 hours. PD eliminates less of the drug than that observed with conventional HD, but due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD. (34)
PEG-IFN α2a	2, 3, 4, 5, 6	≥30 mL/min	No dose adjustment necessary.	No dose adjustment necessary.	80-180 µg every week (42).
		<30 mL/min, TCKD including HD	135 once a week; Monitor for toxicity. If severe adverse reactions or laboratory abnormalities occur, you can reduce the dose to 90 µg once a week until the adverse reactions resolve. If intolerance persists after dose adjustment, discontinue.	Reduce to 135 µg/week. If severe adverse reactions develop, reduce to 90 µg/week. If the intolerance persists, discontinue the therapy. It has not been evaluated in children.	HD: 90-135 once a week (34, 43); 135 µg every 14 días (28).
PEG-IFN α2b	NR	<50 mL/min	Combination with RBV is not recommended. Children: Cr >2 mg/dL: discontinue treatment	Combination with RBV is not recommended.	No data
		30-50 mL/min	Reduce dose by 25% (in monotherapy)*.	Reduce dose by 25%.	
		10-29 mL/min	Reduce dose by 50% (in monotherapy)*.	Reduce dose by 50%.	
		HD	Reduce dose by 50% (in monotherapy).	Reduce dose by 50%.	

* Suspend use if renal functioning decreases during treatment. Cr: creatinine; PD: peritoneal dialysis; TCKD: terminal chronic kidney disease; GNT: genotype; HD: hemodialysis; NR: No report.

Table 3. Results of review of safety and efficacy of drugs for HC in elderly patients with CKD

Medication	GNT	GFR	CKD Stage	Dosage used	Efficacy	ADE	Study type	Mean age ± SD (range)	Ref.
Elbasvir/ grazoprevir	1	15-29 mL/min	4	50/100 mg every 24 hours (No dose adjustment necessary)	SVR12*: 100% (22/22) *HCV RNA <15 IU/mL	Headache, nausea, fatigue, cardiac events (cardiac arrest, myocardial infarction, cardiomyopathy), congestive heart failure, pneumonia, hypertension	C-SURFER: randomized safety trial/ observational efficacy study	Population pharmacokinetics: 58.2 ± 16.8 (NR) Treatment group: 56.5 ± 9.1 (NR) (29)	(29)
		<15 mL/min	5	50/100 mg every 24 hours (No dose adjustment necessary)	SVR12*: 98,9% (93/94) *HCV RNA <15 IU/mL				
Ombitasvir/ paritaprevir/ ritonavir	1	30-89 mL/min	2 y 3	25/150/100 mg every 24 hours (No dose adjustment necessary)	No studies	No data	Pharmacokinetic study	54 (18-71)	(37)
	1b	40,0-164,0 mL/min	1, 2 y 3	25/150/100 mg every 24 hours (No dose adjustment necessary)	No studies	No data	Pharmacokinetic study	61.2 (29.0-76.0)	(38)
	1a, 1b	15-30 mL/min	4	25/150/100 mg every 24 hours (No dose adjustment necessary)	SVR12*: 100% (6/6) *ARN-VHC <25 UI/mL	Fatigue, diarrhea and peripheral edema. Concomitant with RBV: anemia, nausea and headache	Randomized clinical trial	60 (49-69)	(39)
		<15 mL/min o en HD	5	25/150/100 mg every 24 hours (No dose adjustment necessary. They can be administered at any time - before or after – HD.). Limited data, but they suggest that these medications are not extracted by HD.	SVR12*: 85,7% (12/14) *ARN-VHC <25 UI/mL				
	1a	PD	5	12,5/75/50 mg every 24 hours. Less elimination by PD than observed with conventional HD. Due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD.	SVR12: 100% (1/1)	Fatigue, decreased appetite, decreased hemoglobin levels	Case Report	73	(26)
Dasabuvir	1	30-89 mL/min	2 y 3	250 mg every 12 hours (No dose adjustment necessary)	No studies	No data	Pharmacokinetic study	54 (18-71)	(37)
	1a y 1b	15-30 mL/min	4	250 mg every 12 hours (No dose adjustment necessary)	SVR12*: 100% (6/6) *ARN-VHC <25 UI/mL	Fatigue, diarrhea and peripheral edema. Concomitant with RBV: anemia, nausea and headache	Randomized clinical trial	60 (49-69)	(39)
		<15 mL/min o en HD	5	250 mg every 12 hours (No dose adjustment necessary, They can be administered at any time - before or after – HD.). Limited data; but they suggest that these medications are not extracted by HD.	SVR12*: 85,7% (12/14) *ARN-VHC <25 UI/mL				

Table 3. Results of review of safety and efficacy of drugs for HC in elderly patients with CKD. *Continued*

Medication	GNT	GFR	CKD Stage	Dosage used	Efficacy	ADE	Study type	Mean age ± SD (range)	Ref.
Dasabuvir	1a	PD	5	250 mg every 12 hours (No dose adjustment necessary). Less elimination by PD than observed with conventional HD. Due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD.	SVR12: 100% (1/1)	Fatigue, decreased appetite, decreased hemoglobin levels	Case Report	73	(26)
Sofosbuvir	1, 3, 4	HD (8 patients)	5	400 mg every 24 hours (One had dose adjustment at 400 mg every 48 hours and changed simeprevir to daclatasvir)	SVR12*: 90% (9/10) *ARN-VHC <12-15 IU/mL	Thrombocytopenia, pneumonia, fatigue, headache, nausea, myalgia/ arthralgia	Cohort study	50.6 ± 10.9 (31-69)	(9)
		PD (2 patients)		400 mg every 24 hours		Hemolytic anemia, peritonitis, pneumonia, fatigue, headache, nausea, myalgia/ arthralgia			
	1	HD (11 patients)	5	200 mg every 24 hours (1 h before dialysis) Eliminated by dialysis. Dosage of 400 mg: administered 1 h before HD: AUC of sofosbuvir: 28%, GS-331007: 1280%; administered 1 h post-HD: AUC sofosbuvir: GS-331007: 2070%	SVR12*: 83,3% (10/12) *HCV RNA <15 IU/mL.	Fatigue, rash/ itching, anemia, diarrhea, and loss of appetite	Open study	59.7 ± 7.2 (39-77)	(36)
		PD (1 patient)		400 mg every 48 hours					
		8-15 mL/min			SVR12*: 100% (3/3) *HCV RNA <15 IU/mL				
	1	<30 mL/min	4 and 5	400 mg every 24 hours	SVR12: 50% (2/4)	Anemia (in 2 patients with RBV), leukopenia (in 1 patient with PEG-IFN), Glomerular disease of the immune complex similar to lupus with tubulointerstitial nephritis (concomitant RBV with high titers before start of therapy)	Case Series	60 ± 14	(33)
		HD	5	400 mg every 24 hours	SVR12: 100% (2/2)	Anemia (One patient with concomitant RBV treatment)			

Table 3. Results of review of safety and efficacy of drugs for HC in elderly patients with CKD. *Continued*

Medication	GNT	GFR	CKD Stage	Dosage used	Efficacy	ADE	Study type	Mean age ± SD (range)	Ref.
Sofosbuvir	1	<30 mL/min o HD	4 y 5	400 mg every 24 hours (They can be administered at any time - before or after – HD.)	SVR12%: 100% (17/17)	Insomnia, headache, nausea, worsening anemia	Cohort study	57 (46-69)	(27)
	1-6	≤45 mL/min including HD	3B, 4 y 5	400 mg every 24 hours	SVR12: 83% (53/64). All patients with HD achieved SVR.	Fatigue, headache, nausea, anemia, worsening of renal functioning/	Cohort study	NR mean. median. or range. but study included 17 patients older than 65 years with GFR less than 45 mL/ min.	(35)
	1	<30 mL/min (sin HD)	4 y 5	400 mg every 24 hours	SVR12*: 60% (6/10) *HCV RNA <15 IU/mL	Fatigue, renal impairment, pneumonia, anemia, hematemesis	Open study	58 (45-75)	(40)
Simeprevir	1	HD y PD	5	150 mg every 24 hours (No dose adjustment necessary)	SVR12*: 83,3% (10/12) *HCV RNA <15 IU/mL	Fatigue, rash/itching, anemia, diarrhea, and loss of appetite	Open study	59.7 ± 7.2 (39-77)	(36)
		<15 mL/min	5		SVR12*: 100% (3/3) *HCV RNA <15 IU/mL				
	1	15-30 mL/min	4	150 mg every 24 hours (No dose adjustment necessary)	SVR12: 50% (1/2)	No ADE concomitant with sofosbuvir	Case Series	60 ± 14	(33)
		HD	5		SVR12: 100% (1/1)				
	1	<30 mL/min o HD	4 y 5	150 mg every 24 hours (No dose adjustment necessary, They can be administered at any time - before or after – HD.)	SVR12%; 100% (17/17)	Insomnia, headache, nausea, worsening of anemia	Cohort study	57 (46-69)	(27)
Daclatasvir	1b	HD	5	60 mg every 24 hours (No dose adjustment necessary)	SVR12*:100 % (28/28) *HCV RNA <15 IU/mL	Liver damage (re-elevation of serum ALT levels)	Case and control study	65.5 ± 9.5	(16)
	1a, 1b	HD	5	60 mg every 24 hours (No dose adjustment necessary)	SVR12: 95,5 % (20/21)	Nasopharyngitis, pyrexia, loss of appetite, increased ALT, decreased platelets, anemia	Multicentric prospective observational study	63.0 (50-79)	(13)
Asunaprevir	1b	HD	5	100 mg every 12 hours (No dose adjustment necessary)	SVR12*: 100 % (28/28) *HCV RNA <15 IU/mL	Liver damage (re-elevation of serum ALT levels)	Case and control study	65.5 ± 9.5	(16)
	1a, 1b	HD	5	100 mg every 12 hours (No dose adjustment necessary)	SVR12: 95,5 % (20/21)	Nasopharyngitis, pyrexia, loss of appetite, increased ALT, decreased platelets, anemia	Multicentric prospective observational study	63.0 (50-79)	(13)

Table 3. Results of review of safety and efficacy of drugs for HC in elderly patients with CKD. *Continued*

Medication	GNT	GFR	CKD Stage	Dosage used	Efficacy	ADE	Study type	Mean age ± SD (range)	Ref.
RBV	1	<30 mL/min	4 y 5	200 mg every 24 hours y 400 mg every 12 hours	SVR12: 50% (1/2)	Anemia, leukopenia (in 1 patient with PEG-IFN), glomerular disease of the immune complex similar to lupus with tubulointerstitial nephritis (concomitant sofosbuvir, had high titers before start of therapy.)	Case series	60 ± 14	(33)
		HD	5	200 mg every 12 hours	SVR12: 100% (1/1)	Anemia			
	1-3	30-50 mL/min	3	600 mg (adjusted to 200 and 400 mg alternating daily)	No studies	Anemia, changes in mental state, fatigue, headache, nausea, pyrexia, diarrhea, chills and arthralgia (concomitantly with PEG-IFN α2a). RBV dose adjustments due decreased hemoglobin ≤10 g / dL or decrease in the initial value of hemoglobin concentration of ≥3 g/dL, decreased white blood cell and platelet count.	Randomized controlled trial / Pharmacokinetic study	23-65	(41)
		<30 mL/min	4 y 5	200 mg every 24 hours	No studies				
		HD	5	200 mg every 24 hours. Due to large volume of distribution, RBV is not efficiently eliminated by HD because only a small part of the total amount of drug in the body is available to be eliminated by HD.	No studies				
	No data	PD	5	200 mg every 24 hours (subsequently adjusted to 200 mg every 48 hours and discontinued) Less elimination by PD than observed with conventional HD. Due to the continuous nature of PD, cumulative weekly elimination is similar to that observed with intermittent HD.	SVR12: 100% (1/1)	Fatigue, decreased appetite, decreased hemoglobin levels	Case Report	73	(26)
	1b	HD	5	200-400 mg weekly	SVR24*: 73,9% (17/23 PEG-IFNα2a y RBV) *Negativity (<15 UI/mL)	Rejection of non-functional renal allograft, thrombocytopenia with hemorrhagic complications, pneumonia, anemia, pancytopenia (concomitant with PEG-IFN)	Case and control study	52 (25-69)	(34)

Table 3. Results of review of safety and efficacy of drugs for HC in elderly patients with CKD. *Continued*

Medication	GNT	GFR	CKD Stage	Dosage used	Efficacy	ADE	Study type	Mean age ± SD (range)	Ref.
RBV	1a	15-30 mL/min	4	200 mg every 24 hours	SVR12*: 84,6% (11/13) *ARN-VHC <25 UI/mL	Anemia, fatigue, diarrhea, nausea, headache and peripheral edema	Randomized clinical trial	60 (49-69)	(39)
		<15 mL/min o en HD	5	200 mg every 24 hours (They can be administered at any time - before or after – HD.). Minimal extraction by HD.					
	1	<30 mL/min (sin HD)	4 y 5	200 mg every 24 hours	SVR12*: 60% (6/10) *HCV RNA <15 IU/mL	Fatigue, renal impairment, pneumonia, anemia, hematemesis	Open study	58 (45-75)	(40)
	2	HD	5	Initial: 200 mg every 24 hours, subsequently adjusted to 200 mg every 48 hours in days without dialysis	SVR24: 100% (1/1)	Decreased hemoglobin levels	Case Report	67	(28)
PEG-IFN α2a	1a, 1b, 4	38-132 mL/ min	1,2 y 3	135 µg every week (8 patients); 80 µg every week (3 patients) y 180 µg every week (1 patient)	SVR24: 33,3% (4/12)	Leukopenia, asthenia, anemia, thrombocytopenia, depression, hypothyroidism, arthralgia	Case and control study	59.7 (35-74.9)	(42)
	1b, 2a, 2b	HD	5	90-135 µg Once a week	SVR: 33,3% (6/18 cases). SVR not defined	Epistaxis, anemia, neutropenia, thrombocytopenia, depression, interstitial pneumonia	Descriptive study	55.7 ± 11.1 (28-70)	(43)
	1b	HD	5	90-135 once a week (Administered after HD, started at 135 µg/week, then reduced to 90 µg per ADE.)	SVR24*: 50,0% (8/16 in monotherapy). 73.9% (17/23 PEG-IFN α2a and RBV) Total study: 64.1% (25/39) * Negativity (<15 IU / mL)	Rejection of non-functional renal allograft, thrombocytopenia with hemorrhagic complications, pneumonia, anemia, pancytopenia (monotherapy and combined with RBV)	Case and control study	52 (25-69)	(34)
	2	HD	5	Start: 135 µg 1 time a week, subsequently adjusted to 135 µg every 14 days due to platelet reduction.	SVR24: 100% (1/1)	Decreased platelets	Case Report	67	(28)

AUC: area under the curve; ALT: alanine aminotransferase; RNA-HCV: (viral load) ribonucleic acid of hepatitis C virus; PD: peritoneal dialysis; HD: hemodialysis; NR: No report; SVR: sustained virological response.

DISCUSSION

For patients with chronic HC, antiviral treatment is considered essential for preventing complications and improving prognoses, especially when there is evidence of extrahepatic manifestations such as renal alterations that may require dialysis or kidney transplantation. (13, 25) In addition, failure to treat patients who have acquired HCV through dialysis and who are waiting for kidney transplantation can allow HC to progress to HCC adding a need for liver transplantation thus adversely affecting allocation of organs and resources for organ transplantation. (27) Failure to treat HCV infections in patients with CKD reduces patient and graft survival (in cases of transplant patients and transplant candidates) and increases mortality. (8, 12-14, 28, 29)

This review has allowed us to expand the amount of dosing information available for antiviral drugs used to treat HCV in elderly patients with CKD. This information has been structured into a table which may be useful for health professionals involved in prescribing and monitoring these patients. We found information that was not available in UpToDate® and Micromedex®, frequently used databases. This information includes doses of paritaprevir/ombitasvir/ritonavir and dasabuvir for patients with HD and peritoneal dialysis (PD) as well as dosage information for sofosbuvir and simeprevir treatment of patients with GFR less than 30 mL/min who are on either HD or PD. Similarly, the existing information on UpToDate® and Micromedex® has been confirmed for daclatasvir, elbasvir/grazoprevir, PEG-IFN and RBV while information found in UpToDate® on the use of asunaprevir for patients on HD was found to be unsupported because it has not been approved in the United States. This information was not available in Micromedex®.

Among the dosing recommendations that varied the most were those in studies and reports about RBV. Three of the five studies that reported its use in patients with HD showed that doses administered differed from the 200 mg a day recommended in the information of the insert (30) and in the reference databases. (31, 32) For example, Hundemer et al. (33) used 200 mg of RBV every 12 hours for one patient who also received sofosbuvir at full doses. That patient developed anemia that required the use of erythropoietin during antiviral treatment although adjustment or suspension of the medications used was not required. Other authors such as Sperl et al. used reduced doses of RBV of 200 to 400 mg weekly in combination with PEF-IFN α2a. (34) In that study, 73.9% (17 of 23 treated) reached SVR at 24 weeks, and only 9 patients presented worsening of anemia. Eight of the nine required erythropoietin, and one patient required transfusion. Similarly, Hidalgo et al. started treatment with 200 mg a day of RBV together with PEG-IFN but had to reduce the dose of RBV to 200 mg every 48 hours due to decreasing hemoglobin in the patient. (28) In addition, it was necessary to increase the dose of Darbepoetin alfa.

There were also differences among sofosbuvir dosages used in HD or PD patients with GFR <15 mL/min/1.73 m^2. This can be explained by the lack of information in the drug insert and precautions for renal excretion. Beinhardt et al., Hundemer et al., Nazario et al., and Saxena et al. used sofosbuvir doses of 400 mg daily in patients with a GFR <15 mL/min/1.73 m^2 and patients on HD. (9, 33, 27, 35) Bhamidimarri et al. used doses of 400 mg every 48 hours for patients with GFR <15 mL/min/1.73 m2 and 200 mg daily for patients on HD. (36) Only two studies reported the use of sofosbuvir for patients on PD: Beinhardt et al. used full doses while Bhamidimarri et al. adjusted the dose to 400 mg every 48 hours. (9, 36)

Authors such as Bunchorntavakul C et al. (12) have evaluated the treatment of HCV in patients with GFRs <30 mL/min/1.73 m2 who underwent kidney transplantation or who had CKD related to HCV. Based on the information found, they developed strategies for the management of HCV in patients with CKD and TR that use PEG-IFN, RBV, sofosbuvir, simeprevir, boceprevir and telaprevir (The last two have been withdrawn from the market). Similarly, Sorbera et al. produced a table with dosage recommendations for sofosbuvir, simeprevir, ledipasvir, daclatasvir, ombitasvir/paritaprevir and dasabuvir for use in patients with renal impairment. (11)

Unlike the other reviews discussed, this paper presents recommendations about seven therapeutic strategies that use PEG-IFN and RBV and second generation direct acting antivirals: elbasvir/grazoprevir, paritaprevir/ombitasvir/ritonavir, dasabuvir, sofosbuvir, simeprevir, daclatasvir and asunaprevir. We expand the information about the use of sofosbuvir in elderly patients whose GFR is less than 30 mL/min and who are on dialysis. Bunchorntavakul et al. could not include doses for daclatasvir, ombitasvir/paritaprevir, dasabuvir, or elbasvir/grazoprevir since they were not available at the time of their review, and Sorbera et al. neither provided data on the use of asunaprevir at any stage of CKD nor did they provide information on elbasvir/grazoprevir. (12, 11) In addition, those reviews did not report the ages of the patients included in the studies they reviewed, nor did they present information on ADEs which makes it impossible to know the use, dosage and safety of DAAs in elderly patients with CKD.

Treatment of HC in elderly patients with CKD

Preferably, elderly patients with HC and CKD should be treated with drugs that are not excreted by the kidneys to

prevent accumulation of the drugs or their metabolites. On the one hand, elbasvir/grazoprevir, paritaprevir/ombitasvir/ritonavir, dasabuvir, daclatasvir, asunaprevir, ledipasvir and simeprevir are metabolized mainly by the liver while sofosbuvir, the cornerstone of several schemes, has renal excretion (through the inactive metabolite GS-331007). (16, 26, 44) This may limit concomitant use of other DAAs such as ledipasvir, simeprevir and daclatasvir in patients with TCKD. (26)

Currently, the sofosbuvir insert does not contain dosage recommendations for patients whose GFRs are less than 30 mL/min/1.73 m2 or who have TCKD because there is evidence of higher exposures (up to 20 times) of the predominant sofosbuvir metabolite, GS331007. (4, 5) However, studies included in this review have shown the successful use of full doses of sofosbuvir (400 mg every 24 hours) in stages 4 and 5 including treatment of patients on HD and PD without major implications for safety. Also, some of the ADEs reported in patients who used sofosbuvir could be primarily associated with concomitant use of PEG-IFN and/or RBV.

Patients with HD should be considered to eliminate a considerable amount sofosbuvir and its predominant metabolite, (45) but authors who reported the use of full doses of this drug in this population do not provide information on the most appropriate time to administer it. For example, Nazario et al. (27) administered sofosbuvir and simeprevir at any time, before or after dialysis, and achieved SVR 12 in 100% of the patients. ADE was not documented during treatment in 76% (13/17) of the patients. Reported ADEs were insomnia (12%), nausea (5%), headache (5%) and anemia (5%). (27)

In terms of effectiveness, DAAs achieved SVR12 in 83.3% to 100% of the study populations with high cure rates in patients treated with these schemes. Bhamidimarri et al. (36), achieved an SVR12 in 83.3% of their HD and PD patients (10/12) using adjusted dosages of sofosbuvir while they achieved SVR12 of 100% for patients with GFRs between 8 and15 mL/min (3/3).

Several of the ADEs reported in the studies of different drugs may be associated with high prevalences of comorbidities such as hypertension, diabetes mellitus and cardiovascular disease in elderly patients with CKD, especially in patients on dialysis.

This structured review offers systematized information on DAA guidelines used in elderly patients with HC and CKD especially in routine clinical practice as well as information on which schemes have proven to be effective and safe in treated patients. This information can strengthen the processes of prescription and pharmacotherapy follow-up thus contributing to the effectiveness and safety of treatment.

Sofosbuvir is one of the most widely used drugs because it inhibits replication of multiple HCV genotypes, has a high genetic barrier to resistance, is well tolerated and has limited potential for drug-drug interactions. (46) Administration of the full dose (400 mg every 24 hours) in elderly patients with stage 4 and 5 CKD, including those on HD or PD can be considered when none of the schemes that are eliminated through the liver are available (elbasvir/grazoprevir, paritaprevir/ombitasvir/ritonavir/dasabuvir, daclatasvir/asunaprevir) or when they are contraindicated. This is the case for patients with decompensated cirrhosis (Child-Pugh B or C) for whom the use of elbasvir /grazoprevir and paritaprevir/ombitasvir/ritonavir/dasabuvir are not indicated.

Given that, as of publication of this review, Colombian and international clinical practice guidelines have not recommended the use of schemes containing sofosbuvir for patients with stages 4 or 5 CKD, including end-stage renal disease, the recommendations of this review should be considered with caution. The decision to treat HC in elderly patients with CKD, especially stages 4 and 5, should be individualized, should consider available medications, should consider risks and expected benefits of treatment, and should consider the patient's life expectancy and comorbidities. When a decision has been made to use DAAs appropriate dosage adjustments, careful follow-up of renal function, and careful monitoring for the appearance of ADE and SVR are all necessary.

Similarly, the need for prospective safety and effectiveness studies of DAAs for treatment of HCV in elderly patients with CKD is highlighted.

LIMITATIONS

This review has several limitations, and the information in it should be interpreted with caution by prescribing physicians. On one hand, we only searched the PubMed/Medline database while the general recommendation for this type of study is to search in two or more databases. However, the review of the references of the articles included could mitigate this limitation. On the other hand, the articles reviewed include information on patients of various age groups, but usually did not classify data according to age. Consequently, it was not possible to extract the dosing and efficacy information exclusively for patients 65 years or older. Despite this, the studies reviewed show the use of DAAs in this age group which could indicate the absence of problems with their use.

In addition, none of the articles reviewed included information for patients aged 80 and older. Consequently, it is

not possible to make firm recommendations regarding treatment of this population.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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