Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2018; 4, 4: 267–270
DOI: https://doi.org/10.5114/ceh.2018.80129
Received: 20.02.2018, **Accepted:** 10.06.2018, **Published:** 03.12.2018

Original paper

Hepatitis C virus antibodies in outpatients with chronic kidney disease

Lubomir Skladany, Daniela Janceková, Juraj Svac

Department Internal Medicine II of Slovak Medical University, F.D. Roosevelt University Hospital, Banská Bystrica, Slovak Republic

Abstract

Aim of the study: To determine the seroprevalence of hepatitis C virus (HCV) in outpatients with chronic kidney disease (CKD) attending a nephrology clinic.

Material and methods: Prospective observational study on consecutive outpatients attending a nephrology clinic. Inclusion criteria were age > 18 years, CKD, informed consent. There were no exclusion criterias. Recorded variables were age, gender, CKD grade and etiology, anti-HCV antibodies (Ab). Patients with positive HCV Abs were tracked for HCV RNA detection. Study interval was from November 2015 to March 2016. The study has been approved by the Ethic committee of F.D. Roosevelt University Hospital. Funded by Restricted Grant of AbbVie Slovakia.

Results: One hundred and thirty-four patients were enrolled, with median age 70 years (19.7-91), 52% women. CKD grades: G1/2 – 52 patients (39%), G3a – 34 patients (25%), G3b – 32 patients (24%), G4 – 8 patients (6%), G5 – 8 patients (6%); CKD etiology: tubulointerstitial nephritis (TIN) – 53 patients (40%), nephrosclerosis (NS) – 30 patients (22%), diabetic nephropathy (DN) – 23 patients (17%), glomerulonephritis (GN) – 23 patients (17%), others – 5 patients (4%). Anti-HCV antibodies were detected in 8 patients (6%). There were no significant differences in CKD grades between HCV+ and HCV– patients; Heymann nephritis and GN were significantly more frequent in HCV– patients, as was male gender. Of 8 HCV Ab positive patients, 5 were available for HCV RNA testing (2 died after completion of the study, 1 was lost to follow-up); of them, 1 patient tested positive.

Conclusions: Prevalence of anti-HCV antibodies in CKD patients was 6%, which is 4 times higher than in the general population of Slovakia; HCV RNA was detected in 1 patient (12.5%) of anti-HCV positive patients. Based on this result, multicentric, a larger-scale study is considered to be warranted.

Key words: chronic kidney disease, prevalence, hepatitis C virus infection.

Address for correspondence

Dr. Daniela Janceková, Department Internal Medicine II of Slovak Medical University, F.D. Roosevelt University Hospital, Námestie L. Svobodu 1, 97401 Banská Bystrica, Slovak Republic, e-mail: daniela.jancekova@gmail.com

Introduction

With 1.5% seroprevalence of hepatitis C virus (HCV) infection in the general population, 10% identified cases, and < 2% treatment rate, Slovakia belongs to the countries with low-to-medium prevalence, a low diagnosis rate, and a very low treatment rate, respectively [1]. Introduction of directly acting antivirals (DAA) with a high rate of sustained virological response (SVR), and a very good safety profile, has led to removal of patients with chronic kidney disease (CKD) from the "difficult-to-treat" (DTT) list [2]. CKD affects 10%, and HCV 2.5% of adults from the general population [3]. There is a paucity of data on the prevalence of HCV in CKD (especially of grades ≤ 4), despite their known bidirectional relationship: HCV increases the risk of CKD by 40%, which has been accepted inasmuch that professional societies issued guidelines recommending screening all HCV infected patients for CKD [4-13]. *Vice versa*, CKD increases the risk of HCV infection, mainly in the stages previously known as end-stage renal disease (ESRD), with seroprevalence of 7.5% [3, 14-16].

Aim of the study

To determine the prevalence of antibodies to HCV in consecutive outpatients with CKD of any grade.

Material and methods

Prospective cohort study of consecutive incomers to the Nephrology Outpatient Clinic. Inclusion criteria were age > 18 years, informed consent and CKD according to KDIQO [29]. There were no exclusion criterias. Study interval was from November 2015 to March 2016. Recorded variables were gender, age, etiology of CKD, stage of CKD (G1-G5) and anti-HCV antibodies (ELISA – 3rd generation, Cobase 411, Roche). Detection of HCV RNA was not part of the original protocol; after completion of the study, anti-HCV positive patients were contacted and invited with this intent. Funding: This study was supported by a restricted grant of AbbVie Slovakia. The study was approved by the institutional ethics committee, and conducted in agreement with the Declaration of Helsinki.

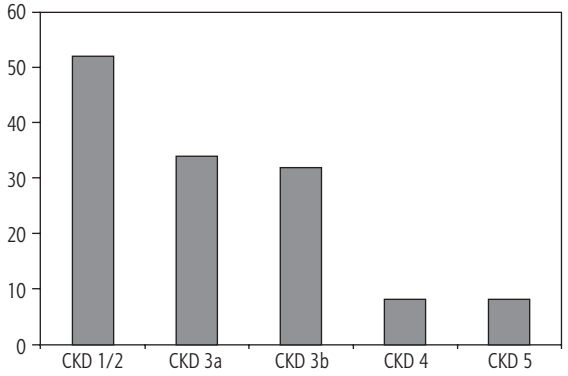

Fig. 1. Number of patients in different chronic kidney disease (CKD) grades

Table 1. Baseline characteristics and hepatitis C virus – antibody status in 134 outpatients with chronic kidney disease

	Whole cohort	HCV– *n* (%)	HCV+ *n* (%)	*p*
No. of patients	134	126	8	–
Age (median)	70 (19.7-91)	70 (19.7-91)	61 (31-78)	0.08
Gender – female	70 (52%)	67 (53%)	3 (37%)	0.04
Grade CKD				
G1-G2	52 (39%)	48 (38%)	4 (50%)	0.08
G3a	34 (25%)	33 (26%)	1 (12.5%)	ns
G3b	32 (24%)	31 (24%)	1 (12.5%)	ns
G4	8 (6%)	7 (6%)	1 (12.5%)	0.13
G5	8 (6%)	7 (6%)	1 (12.5%)	0.13
Etiology CKD				
TIN	53 (40%)	50 (40%)	3 (37.5%)	0.06
NS	30 (22%)	29 (23%)	1 (12.5%)	0.03
DN	23 (17%)	21 (17%)	2 (25%)	0.09
GN	23 (17%)	22 (17%)	1 (12.5%)	0.04
Others	5 (4%)	4 (3%)	1 (12.5%)	0.20

HCV – hepatitis C virus; CKD – chronic kidney disease; TIN – tubulointerstitial nephritis, NS – nephrosclerosis; DN – diabetic nephropathy; GN – glomerulonephritis

Results

During the study interval of 5 months, 134 patients with CKD were recruited; female – 70 patients (52%), median age – 70 years (19.7-91). Grades of CKD were as follows: G1/2 – 52 patients (39%), G3a – 34 (25%), G3b – 32 (24%), G4 – 8 (6%), G5 – 8 (6%) (Fig. 1). Etiology of CKD: tubulointerstitial nephritis (TIN) – 53 patients (40%), nephrosclerosis (NS) – 30 (22%), diabetic nephropathy (DN) – 23 (17%), glomerulonephritis (GN) – 23 (17%), others – 5 (4%). Anti-HCV antibodies were detected in 8 patients (6%), 3 women (37.5%), median age 61 years (31-78). Grades of CKD in anti-HCV positive patients did not differ from their anti-HCV negative counterparts (Table 1). Etiology of CKD (HCV+ vs. HCV– patients): TIN – 3 patients (37.5%) vs. 50 patients (40%) ($p = 0.06$); DN – 2 (25%) vs. 21 (17%) ($p = 0.09$); GN – 1 (12.5%) vs. 22 patients (17%) ($p = 0.04$), NS – 1 (12.5%) vs. 29 patients (23%) ($p = 0.03$), others – 1 patient (12.5%) vs. 4 patients (3%) ($p = 0.20$) (Table 1). Eight anti-HCV positive patients were approached after the completion of the protocol with attempt to determine HCV-RNA; 2 of them died before location, and 1 was lost to follow-up. Of the remaining 5 patients, HCV RNA was detected in 1 (20%); this patient was treated with DAA and achieved an SVR.

Discussion

In contrast to CKD 5, data on HCV infection in lower stages are scarce. Although the global impact of HCV infection on the prognosis of patients with CKD has been considered negligible in stage 3, and questionable in stage 4, the consequences can still be devastating – in individual cases due to the association of HCV with the pathogenesis of CKD, and in all after kidney transplantation (RTx) [21-24]. Before the introduction of DAA, therapy of HCV infection in ESRD and RTx patients had been more than problematic, with only 1% to 5% receiving interferon IFN-based therapy [16, 25]. Nowadays, CKD and renal replacement therapy patients with HCV infection should be indicated (where feasible), and prioritized (where indicated) for the therapy with IFN- and ribavirin-free DAA regimens [2, 26, 27]. DAA have even enabled a safe RTx of HCV positive kidneys to HCV negative recipients [28].

Table 2. Seroprevalence of hepatitis C virus infection (HCV) in patients with end-stage renal disease in Slovakia

Author, year	Context	Number of patients	Dg modality	Prevalence
Javorsky and Skladany, 1997	Single-center, cross-sectional, HDU	NR	Anti-HCV 2	30% (genotype 1b: 85%)
Skladany, 1997-1999	Multicentric (nationwide), cross-sectional, HDU	2686	Anti-HCV 2	12.8%
Šváč, 2006	Multicentric, cross-sectional, HDU	749	Anti-HCV 3	5%
Javorský, 2015	Multicentric, cross-sectional, HDU	1064	Anti-HCV 3	2.5%
Lackova, 2015	Waiting-list RTx	365	Anti-HCV 3	2.5%

HDU – hemodialysis unit; Anti-HCV – antibodies to hepatitis C virus, number denotes the generation of the ELISA test; RTx – kidney transplantation; NR – not reported; Dg – diagnostic modality

Studies in Slovak hemodialysis unit (HDUs) from the years 1995, 1997–1999, 2006, and 2015 yielded HCV antibody seroprevalence of 30%, 12.8%, 5%, and 2.5%, respectively (Table 2) [17]. In patients on the waiting list for RTx, the seroprevalence was 2.5% [18]. These results are in accord with decreasing trends from the USA and the European Union [15, 19, 20]. In contrast to these CKD 5 data, those on stages 1-4 are scarce.

To the best of our knowledge, this pilot study is the first of its kind in this region. It has several limitations: i) the setting is a tertiary referral center with a possibility of selection bias; ii) small sample size; iii) lack of more prospective information on the anti-HCV positive cases in terms of viremia, genotype, liver fibrosis, etc. The study is relatively strong in its prospective design, and a strict adherence to the diagnostic criteria of CKD [29]. If the 1.5% figure would be taken as the reference value of anti-HCV antibodies' prevalence in the general population, the 6% prevalence in patients with CKD would be 4-fold increased over the baseline [1]. Unfortunately, our patients were not examined for the presence of HCV RNA immediately after the detection of HCV antibodies, which has led to the loss of 3 of them; of the remaining 5 patients, HCV RNA was detected in only one (20%). This figure is very difficult to interpret, since there are very few data on the anti-HCV:HCV RNA ratio in CKD < 5. In our previous study in hemodialyzed patients, HCV RNA positivity was found in 29 of 38 anti-HCV positive patients (76%) (unpublished data). The most likely explanation for the very low rate of HCV RNA positivity in anti-HCV positive CKD patients is the small number of patients. Since the study was neither designed nor powered to analyze the risk factors for HCV infection, or associations of HCV with the etiology of CKD, one can turn to the results of the meta-analysis by Fabizi *et al.* [30]. Of note in our cohort are the counterintuitive associations of GN and NS with HCV seronegativity, and the lack of an association of HCV seropositivity with DN; these observations, or lack of them, deserve more attention in the future. The 88% prevalence of CKD < 4 is reassuring as to the main aim of the study (Fig. 1). As the data from regional HDUs have shown a steady decline in the HCV seroprevalence over the last 20 years, it would be of interest to determine whether these dynamics would by paralleled in a cohort with CKD < 5.

Conclusions

In this pilot study on outpatients with CKD, the prevalence of anti-HCV antibodies was 6%, which is 4 times higher than in the general population. Considering the low HCV infection diagnosis/awareness rates in the region, a cohort with CKD could be scrutinized as the possible target for systematic screening. Preceding such an endeavor, our results should be corroborated in larger-scale, multicentric projects.

Disclosure

All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. An independent ethics committee reviewed and approved the protocol.

This study was supported by a restricted grant of AbbVie, AbbVie s.r.o.

Conflicts of interest (D. F. Thompson, *Understanding Financial Conflicts of Interest*, 1993). LS reports having received consultancy and speaker honoraria from AbbVie, Gilead, MSD, DJ reports having received speaker honoraria from AbbVie, JŠ reports no conflict of interest.

References

1. Schréter I, Kristian P, Klement C, et al. Prevalencia infekcie vírusom hepatitídy C v Slovenskej republike. Klin Mikrobiol Inf Lék 2007; 13: 54-58.
2. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017; 66: 153-194.
3. Fabrizi F, Martin P, Messa P. New treatment for hepatitis C in chronic kidney disease, dialysis, and transplant. Kidney Int 2016; 89: 988-994.

4. Tsui JI, Vittinghoff E, Shlipak MG, et al. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol 2006; 17: 1168-1174.
5. Tsui, JI, Vittinghoff E, Shlipak MG, et al. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. Arch Intern Med 2007; 167: 1271-1276.
6. Li WC, Lee YY, Chen IC, et al. Age and gender differences in the relationship between hepatitis C infection and all stages of chronic kidney disease. J Viral Hepat 2014; 21: 706-715.
7. Chen YC, Lin HY, Li CY, et al. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. Kidney Int 2014; 85: 1200-1207.
8. Lee JJ, Lin MY, Yang YH, et al. Association of hepatitis C and B virus infection with CKD in an endemic area in Taiwan: a cross-sectional study. Am J Kidney Dis 2010; 56: 23-31.
9. Fabrizi F, Verdesca S, Messa P, et al. Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis. Dig Dis Sci 2015; 60: 3801-3813.
10. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int Suppl 2008; 109: S1-S99.
11. Omata M, KandaT, Wei L, et al. APASL consensus statements and recommendations for hepatitis C prevention, epidemiology, and laboratory testing. Hepatol Int 2016; 10: 681-701.
12. Spustová V. Definícia, hodnotenie a klasifikácia chronického ochorenia obličiek. Via Pract 2010; 7: 152-154.
13. Gragnani L, Fognani E, Piluso A, et al. Hepatitis C virus-related mixed cryoglobulinemia: is genetics to blame? World J Gastroenterol 2013; 19: 8910-8915.
14. Patel PR, Thompson ND, Kallen AJ, et al. Epidemiology, surveillance, and prevention of hepatitis C virus infections in hemodialysis patients. Am J Kidney Dis 2010; 56: 371-378.
15. Jadoul M, Poignet JL, Geddes C, et al. The changing epidemiology of hepatitis C virus (HCV) infection in haemodialysis: European multicentre study. Nephrol Dial Transplant 2004; 19: 904-909.
16. Goodkin DA, Bieber B, Jadoul M, et al. Mortality, hospitalization, and quality of life among patients with hepatitis C infection on hemodialysis. Clin J Am Soc Nephrol 2017; 12: 287-297.
17. Skladaný Ľ, Šváč J, Lacková E, et al. Hepatitída C u pacientov s chronickou nedostatočnosťou obličiek liečenou hemodialýzou alebo transplantáciou obličky. Trend Hepatol 2010; 2: 3-12.
18. Lackova E. Indukcia u anti-HCV pozitívnych príjemcov obličky. Farmakoterapia v praxi 2015; suppl. 3/2015.
19. Finelli L, Miller JT, Tokars JI, et al. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial 2005; 18: 52-61.
20. Chacko EC, Surrun SK, Mubarack Sani TP, et al. Chronic viral hepatitis and chronic kidney disease. Postgrad Med J 2010; 86: 486-792.
21. Mathurin P, Mouquet C, Poynard T, et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 1999; 29: 257-263.
22. Latt N, Alachkar N, Gurakar A. Hepatitis C Virus and its renal manifestations: a review and update. Gastroenterol Hepatol (NY) 2012; 8: 434-445.
23. Fabrizio F. Hepatitis C virus, cryoglobulinemia, and kidney: novel evidence. Scientifica (Cairo) 2012; 2012: 128382.
24. Reddy KR, Roth D, Bruchfeld A, et al. Elbasvir/grazoprevir does not worsen renal function in patients with hepatitis C virus infection and pre-existing renal disease. Hepatol Res 2017; 47: 1340-1345.
25. Sperl J, Frankova S, Senkerikova R, et al. Relevance of low viral load in haemodialysed patients with chronic hepatitis C virus infection. World J Gastroenterol 2015; 21: 5496-5504.
26. Colombo M, Aghemo A, Liu H, et al. Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic hepatitis C virus genotype 1 or 4 infection: a randomized trial. Ann Intern Med 2017; 166: 109-117.
27. Sperl J, Frankova S, Kreidlova M, et al. Combination of sofosbuvir and daclatasvir in the treatment of genotype 3 chronic hepatitis C virus infection in patients on maintenance hemodialysis. Ther Clin Risk Manag 2017; 13: 733-738.
28. Goldberg DS, Abt PL, Blumberg EA, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. N Engl J Med 2017; 376: 2394-2395.
29. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014; 85: 49-61.
30. Fabrizi F, Martin P, Dixit V, et al. Hepatitis C virus infection and kidney disease: a meta-analysis. Clin J Am Soc Nephrol 2012; 7: 549-557.