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Tratamento da hepatite C crônica em pacientes renais crônicos com esquemas contendo sofosbuvir

Porto Alegre 2019

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Dissertação submetida ao Programa de Pós-Graduação em Hepatologia da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Mestre

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RESUMO

Introdução: Pacientes com insuficiência renal crônica (IRC) representam uma população de importante risco de contaminação pelo vírus da hepatite C (VHC) e apresentam pior prognóstico na evolução da doença hepática e renal. O avanço no tratamento do VHC mudou drasticamente o tratamento da hepatite crônica pelo VHC, principalmente nessa população de doentes.

Objetivos: Analisar a segurança e efetividade de regimes contendo sofosbuvir no tratamento do VHC em pacientes com doença renal crônica; avaliar o perfil clínico e epidemiológico dos pacientes renais crônicos ou transplantados renais portadores de hepatite crônica pelo VHC

Métodos: Estudo observacional, retrospectivo, realizado em portadores do VHC e IRC maiores de 18 anos. Foram avaliados a taxa de filtração glomerular pré, pós e 3 meses após o termino do tratamento, presença de transplante renal, genótipo do VHC, grau de fibrose hepática, existência de comorbidades, uso de imunossupressores, regimes de tratamento indicado para VCH e resposta virológica sustentada (RVS), avaliada 12 semanas após o final de tratamento. Na análise estatística, o nível de significância adotado foi de 5% ($p<0.05\%$)

Resultados: Setenta pacientes foram analisados. Houve predomínio de homens, a maioria havia realizado transplante renal e apresentava perda moderada da função renal, eram portadores do genótipo 1 do VHC e não cirróticos. Trinta e cinco pacientes foram tratados com esquema contendo sofosbuvir, sendo o regime mais indicado a associação com daclatasvir por 12 semanas de tratamento. A RVS por intenção de tratamento foi 88,6% e por protocolo foi

96,9%. O tratamento foi interrompido em 1 (2.85%) paciente por anemia e em 2 (5.7%) por perda da função renal.

Conclusão: O tratamento da infecção crônica pelo VHC em pacientes com IRC com esquemas contendo sofosbuvir é seguro e efetivo, com RVS12 de 88,6%. A maioria dos pacientes avaliados era composta por não cirróticos, transplantados renais, portadores do genótipo 1 do VHC, em uso de imunossupressores, com comorbidades e potenciais interações medicamentosas, compondo uma população especial de doentes a serem tratados.

ABSTRACT

Introduction: Patients with chronic kidney disease (CKD) represent a population at high risk for chronic hepatitis C vírus (VHC) infection and have a worse prognosis in the evolution of liver and kidney disease. The advancement of treatment of HCV dramatically changed the treatment of chronic VHC mainly in this special population.

Objectives: To analyze the safety and efficacy of Sofosbuvir-containing regimens in VHC treatment in CKD. In addition, to outlining the clinical and epidemiological profile of chronic renal or renal transplant patients with chronic VHC infection.

Methods: Retrospective observational study performed in patients with VHC and CKD over 18 years of age. Renal function was accessed by serum creatinine and glomerular filtration rate (GFR) pre, post, and 3 months after the end of VHC treatment, presence of renal transplantation, VHC genotype, liver fibrosis degree, existence of comorbidities, use of immunosuppressants, treatment regimens for VHC and sustained virological response (SVR) after 12 weeks of treatment. In the statistical analysis, the level of significance was 5% ($p < 0.05\%$)

Results: Seventy patients were analyzed, and were predominantly male renal transplant patients with moderate loss of renal function, non-cirrhotic VHC genotype 1 patients. The most indicated HCV treatment regimen was sofosbuvir and daclatasvir for twelve weeks of treatment. Thirty-five patients were treated with a sofosbuvir-containing regimen and achieved SVR in 88.6% (intention to treat analyses) and 96,9% (per protocol analyses). Treatment was interrupted in 1 (2.85%) patient due to anemia and in 2 (5.7%) due to loss of renal function.

Conclusion: The treatment of chronic VHC infection in patients with CKD with schemes containing Sofosbuvir is safe and effective, with RVS12 of 88,6%. Most of the patients evaluated were non-cirrhotic patients, renal transplant patients with HCV genotype 1, immunosuppressants, comorbidities, and potential drug interactions, making up a special population of patients to be treated.

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LISTA DE SIGLAS E ABREVIATURAS

AASLD: Associação Americana para Estudos das Doenças do Fígado
FA: Fibrilação Atrial
ALT: Alanina aminotransferase
ANOVA: Análise de variância

APRI: AST to platelet ratio index (Índice de Relação Aspartato aminotransferase sobre Plaquetas)
AST: Aspartato aminotransferase
AZA: Azatioprina
ICC: Insuficiência cardíaca congestiva

CYA: Ciclosporina

Com: comorbidades
Cr: creatinina
CrCl: Clearance de creatinina
CTP: Child-Turcotte-Pugh

DAA: direct-acting antiviral (antivirais de ação direta)

DM: diabetes mellitus

DRC: Doença renal crônica

EASL: Associação Europeia para o Estudo do Fígado

FDA: Admistração de Comidas e remédios

FK: Tracolimus

Gen: Genótipo

GESF: Glomeruloesclerose segmentar e focal

GFR: Taxa de filtração glomerular

GNMP: Glomerulonefrite menbranoproliferativa

HAS: Hipertensão arterial sistemica

HIV: Vírus da imunodeficiência humana

IC: Intervalo de confiança

IDSA: Sociedade de Doenças infecciosas da América

IFN: Interferon convencional

KDIGO: Kidney Disease Improving Global Outocomes

MMF: Micofenolato de mofetil

Mtor: Alvo da rapamicina em mamíferos

NS3/4A: Nonstructural protein 3/4A

NS5A: Proteína não estrutural 5A

NS5B: Proteína não estrutural 5B

PCR: Reação em cadeia da polimerase

PEG- IFN: Peginterferon

RBV: Ribavirina

RVS: Resposta virológica sustentada

SOF: Sofosbuvir

TFG: Taxa de filtração glomerular

THE: Elastografia hepática transitória

VHB: Vírus da hepatite B

VHC: Vírus da hepatite C

SUMÁRIO

1.REVISÃO DA LITERATURA

1.1 Epidemiologia da hepatite C crônica em pacientes renais crônico

A prevalência da infecção pelo vírus da hepatite C (VHC) em pacientes com doença renal varia entre os centros mundiais de diálise, mas é claramente superior à da população geral (1,2). Um estudo multicêntrico (n=1710) mostrou a prevalência de hepatite C em pacientes dialíticos, em 2012, na Itália de 11,5%, Estados Unidos de 7,3%, França de 6,9%, Alemanha de 4,5% e Canadá de 4,1%(2)

Embora a prevalência e incidência da infecção pelo VHC entre pacientes com insuficiência renal em diálise tenha diminuído nas últimas décadas, estima-se uma incidência de 0,2% a 15% ao ano nesses pacientes em países europeus (3).

Existem vários fatores que são relacionados com as altas taxas de prevalência, como transfusões de sangue, uso de drogas ilícitas injetáveis, o período de tempo que o paciente está em hemodiálise, entre outros (4,5).

No Brasil, 1,38% da população geral está infectada com o VHC. O percentual de expostos ao VHC na faixa etária de 10 a 19 é de 0,75% (IC 95% 0,53% - 0,98%) e de 1,56% (IC 95% 1,28% - 1,91%) para o grupo de 20 a 69 anos (6). De acordo com o Censo 2016 da Sociedade Brasileira de Nefrologia, o Brasil tem uma prevalência da infecção pelo VHC entre pacientes em hemodiálise de 4,2% a 3,7% (7).

O genótipo 1a é predominante entre pacientes hemodialisados, seguido pelos genótipos 1b e 3a (8, 9,10). Entretanto, dois estudos, um realizado em

Belo Horizonte / MG e outro em Rio Grande/ RS, mostraram que o subtipo 2b representa o segundo subtipo predominante (11,12).

1.2 Rastreamento de hepatite C crônica em pacientes renais crônicos

A maioria da população portadora de infecção crônica pelo VHC é assintomática. É recomendável coletar o anti-HCV e realizar a confirmação da viremia através da reação em cadeia da polimerase do VHC (PCR-VHC) antes da sessão de hemodiálise devido esse procedimento reduzir a viremia e apresentar um resultado falso negativo (13). É importante realizar o diagnóstico precoce de infecção por VHC atráves do rastreamento frequente. A *Kidney Disease Improving Global Outocomes* (KDIGO) recomenda a coleta de anti-HCV a cada 6 meses em todos os pacientes em centros de hemodiálise e diálise peritoneal ou que apresentem alteração de alanina aminotransferase (ALT). Nos portadores que já realizaram o tratamento para VHC, recomendam coletar PCR-VHC a cada 6 meses devido risco de reinfecção (14). A recomendação atual do Ministério da Saúde do Brasil é de rastreamento trimestral (15). A monitorização do nível sérico de ALT deve ser realizada mensalmente em todos os pacientes. Porém, os níveis de ALT não mudam com frequência em pacientes com VHC em hemodiálise, sugerindo que as aminotransferases não são bons preditores de lesão hepatocelular nesses pacientes, pois há inibição enzimática por toxinas urêmicas, deficiência de piridoxina, perda de enzimas em diálise e interferência de outras substâncias dialisáveis na dosagem de aminotransferases (14).

1.3 Influência do VHC em pacientes renais crônicos

A infecção pelo VHC em doentes com doença renal é associada a mais rápida progressão da doença hepática, mortalidade devido a complicações da cirrose e diminuição da sobrevida (16,17). Uma metanálise sobre o impacto da infecção pelo VHC na sobrevida dos pacientes em diálise (7 estudos; n =11.589) mostrou um risco relativo estimado para a mortalidade de 1,34 (intervalo de confiança de 95% 1,13-1,59) (18). Nos pacientes transplantados renais, o VHC tem um impacto negativo na sobrevida dos pacientes devido ao risco de perda do enxerto por rejeição e doença glomerular induzida pelo vírus, infecções, diabetes pós-transplante, câncer e rápida progressão da fibrose hepática (14). Os transplantados renais com cirrose muitas vezes evoluem com a perda do enxerto renal, especialmente se não tratado o VHC. Por isso deve ser considerado transplante duplo (hepático e renal) nos cirróticos em hemodiálise (14). O estadiamento da fibrose hepática através de biópsia hepática ou métodos não invasivos é recomendado em todos os candidatos a transplante renal, embora o tratamento possa ser realizado independentemente dessa avaliação (14). Os métodos não invasivos apresentam uma precisão semelhante à biópsia hepática em pacientes com com doença renal crônica (DRC) em comparação com a população em geral, e a *KDIGO* recomenda a avaliação inicial da fibrose hepática por métodos não invasivos. Os objetivos da análise do grau de fibrose são decidir o tempo de tratamento com DAA e diagnosticar a cirrose, além de considerar o transplante renal isolado para cirrose compensada e transplante duplo (hepático e renal) em cirróticos descompensados. Para decidir quando tratar o VHC em candidatos a tranplante renal (antes ou após o transplante) é importante conhecer o grau de fibrose, o genótipo do VHC e o tempo de espera

na fila de transplante. Pacientes sem fibrose (F0) e com expectativa de transplantar em até 24 semanas podem ser tratados do VHC após o transplante (figura1) (14).

A infecção pelo vírus da hepatite C também pode ser responsável pelo agravamento da função renal e outras manifestações extra-hepáticas, como linfoma, crioglobulinemia e aterosclerose (19). Portanto, recomenda-se monitorar a função renal de todos os infectados pelo VHC (14). Fabrizi e col (20) demonstraram que os pacientes com VHC tiveram um aumento de 27% no risco de DRC em comparação com os pacientes sem VHC. Este estudo também revelou que os pacientes positivos para o VHC tiveram um risco 2 vezes maior de glomerulonefrite membranoproliferativa (GNMP) e um risco quase 17 vezes maior de crioglobulinemia (20).

1.4 Tratamento com PEG e ribavirina em pacientes renais crônicos

O tratamento da hepatite C evoluiu rapidamente ao longo dos últimos anos. A associação de peginterferon (PEG-IFN) e ribavirina (RBV) a antivirais de ação direta (DAA) mostrou que a epidemiologia, a história natural e a resposta ao tratamento do VHC variam entre certas populações de pacientes, especialmente naqueles com descompensação da cirrose, os transplantados, os com doença renal em fase terminal e os coinfectados com vírus da imunodeficiência humana (HIV) (21). O manejo da infecção pelo do VHC nessas populações especiais é um desafio, especialmente com a terapia a base de PEG-IFN, pela reduzida eficácia do tratamento, aumento dos efeitos colaterais e alteração da farmacocinética. Um *clearance* de creatinina (CrCl) abaixo de 30

mL/min aumenta a concentração plasmática do IFN em aproximadamente 90% e a meia vida é aumentada cerca de 40% (22). A ribavirina é excretada principalmente por via renal, de modo que a sua concentração plasmática aumenta em mais do que duas vezes em doentes com insuficiência renal moderada a grave.

A monoterapia com PEG-IFN é eficaz para pacientes portadores de VHC com insuficiência renal terminal, com taxas de resposta virológica sustentada (RVS) de 33% a 41% e taxas de abandono de 17% a 30% (22). Um estudo (23) randomizado de 205 pacientes portadores do VHC com insuficiência renal terminal revelou que a adição de uma dose baixa de RBV ao tratamento com PEG-IFN foi associada com maiores taxas de RVS (64% vs 33% p <0,001) e anemia severa (hemoglobina <8,5 g/dL) (72% vs 6%, p <0,001), com comparável taxa de abandono (7% vs 4%, não significativo) (23). Com o ajuste da dose e cuidadoso acompanhamento, o tratamento com PEG-IFN mais RBV em pacientes com o VHC e doença renal terminal pode ser associado com taxas de RVS semelhantes com aquelas de pacientes com função renal normal (23). Porém, em pacientes com doença renal crônica com *clearance* de creatinina menor que 15 mL/min ou diálise não se recomenda adicionar ribavirina ao tratamento conforme a KDIGO (14). Além disso, o tratamento com IFN é, frequentemente, ineficaz em receptores de transplante renal e pode estar associada com um risco elevado de rejeição do enxerto (15 a 100%) (21). Portanto, a terapia a base de IFN só deve ser iniciada em pacientes transplantados renais em situações específicas, tais como a hepatite colestática fibrosante, glomerulonefrite grave ou quando o risco de não tratamento da

infecção pelo VHC for superior ao risco de complicações e não se tenha disponível os antiviriais de ação direta (DAA) (24).

1.5 Tratamento com DAA em pacientes renais crônicos

No final de 2013, a *Food and Drug Administration* (FDA) aprovou nos EUA dois DAA, sofosbuvir e simeprevir, para o tratamento da hepatite C crônica (25,26) e em meados de 2015 o daclatasvir (27). O sofosbuvir foi o primeiro DAA aprovado, um inibidor da polimerase codificada pela região NS5B do HCV, para o tratamento do vírus C, genótipos 1, 2, 3 e 4. Com a eficácia pangenotípica pode eliminar a necessidade da associação com interferon. Os eventos adversos mais comuns (≥ 20%) relatados em pacientes recebendo sofosbuvir em combinação com ribavirina foram fadiga e cefaléia. Os niveis de sofosbuvir e GS331007 (seu metabólito ativo) são substancialmente mais elevados em pacientes com insuficiência renal grave (taxa de filtração glomerular < 30 mL/min) ou doença renal terminal em hemodiálise. Com base nos dados disponíveis, a orientação é de que nenhuma redução da dose é necessária para utilizar sofosbuvir em pacientes portadores de VHC com leve a moderada perda da função renal (CrCl> 30 mL/min). Porém, o uso da dose plena (400 mg) de sofosbuvir não é aprovado para pacientes com Crcl abaixo de 30 mL / min ou em diálise devido toxicidade cardiovascular e hepatobiliar diagnosticadas em testes com animais. O uso da dose reduzida (200 mg) é baseado na hipótese de que a exposição ao derivado do nucleosídeo livre deverá ser maior em pacientes com insuficiência renal terminal, e que a redução da dose pela metade representaria uma abordagem segura e clinicamente prática para diminuir a toxicidade potencial, oferecendo

uma chance razoável de eficácia. Portanto, o uso da dose reduzida e plena de sofosbuvir nesta configuração continua a ser estudada (28,29). O simeprevir é um antiviral de segunda geração que inibe a protease codificada pela região NS3 / 4A do VHC, indicado para o tratamento do genotipo 1. A dose padrão recomendada é de uma cápsula de 150 mg tomado por via oral uma vez ao dia. A segurança e eficácia de simeprevir não foram estudadas na doença renal terminal. No entanto, como simeprevir é predominantemente eliminado nas fezes por excreção biliar, postula-se que uma dose padrão é provável que seja segura em doentes em hemodiálise. As reações adversas atribuidas ao simeprevir são exantema, prurido, náuseas (24). O daclatasvir é um inibidor da polimerase codificada pela região NS5A do VHC, que tem demonstrado potente efeito antiviral e eficácia clínica entre múltiplos genótipos. Sua dose padrão é 60 mg uma vez dia, e não necessita ser ajustada para função renal ou hepática. Porém se recomenda 90 mg quando tratados pacientes em uso de efavirenz, etravirina ou nevirapina e 30 mg em associação com atazanavir/ritonavir ou atazanavir /cobicistate devido a interações medicamentosas. É geralmente seguro, bem tolerado e tem baixa resistência. Efeitos colaterais mais comuns são fadiga e cefaléia (26).

Recentemente, os dados de segurança e eficácia dos DAA em populações especiais portadores do VHC tem sido cada vez mais avaliados. Embora o número de pacientes seja ainda limitado em ensaios clínicos, estes dados são promissores, o que levou a uma recomendação para seu uso publicadas pela Associação Americana para o Estudo das Doenças do Figado (*American Association for the Study of Liver Diseases* – AASLD) (28) e a Associação

Europeia para o Estudo do Fígado (*European Association for Study of the Liver* - EASL) (29).

Saxena e col (30) observaram, no estudo TARGET (n=19, sendo 5 em hemodiálise), RVS semelhante entre os grupos com diferentes níveis de função renal quando tratados com sofosbuvir 400 mg/dia (RVS 100%). Contudo, pacientes com Crcl <30 mL/min experimentaram mais efeitos colaterais, como anemia, insuficiência renal aguda e piora da função renal (24%). Assim, a dose ótima de sofosbuvir a ser usada em pacientes renais graves precisa ser esclarecida. Uma série de casos (31) analisou 17 pacientes (15 em hemodiálise e 2 pacientes com Crcl < 30 mL/mim) tratados com sofosbuvir e simeprevir em dose plena por 12 semanas, sem ribavirina. Todos os pacientes obtiveram RVS na quarta e décima segunda semana pós-tratamento (RVS 100%). Não houve efeitos colaterais importantes, 24% apresentaram sintomas leves, como por exemplo, insônia, cefaleia e náuseas. Anemia severa ocorreu somente em um paciente que necessitou transfusão sanguínea. Bhamidimarri e col (32) compararam a dosagem de 200 mg de sofosbuvir ao dia versus 400 mg a cada dois dias, com dose plena de simeprevir. Esse estudo (n = 15; sendo 12 em hemodiálise) obteve RVS de 91 e 75%, respectivamente. Desnoyer e col (33) observaram em 12 pacientes em diálise, que sofosbuvir 400 mg, por dia ou apenas no dia de hemodiálise foi bem tolerado, sem perda de função renal. A RVS foi de 100% em pacientes que usaram sofosbuvir todos os dias e 60% nos que receberam três vezes na semana. Singh e col (34) estudaram pacientes em hemodiálise (n =8) que receberam dose plena de 400 mg de sofosbuvir, observando RVS em 87,5% dos casos. Dumortier e col (35) mostraram que o

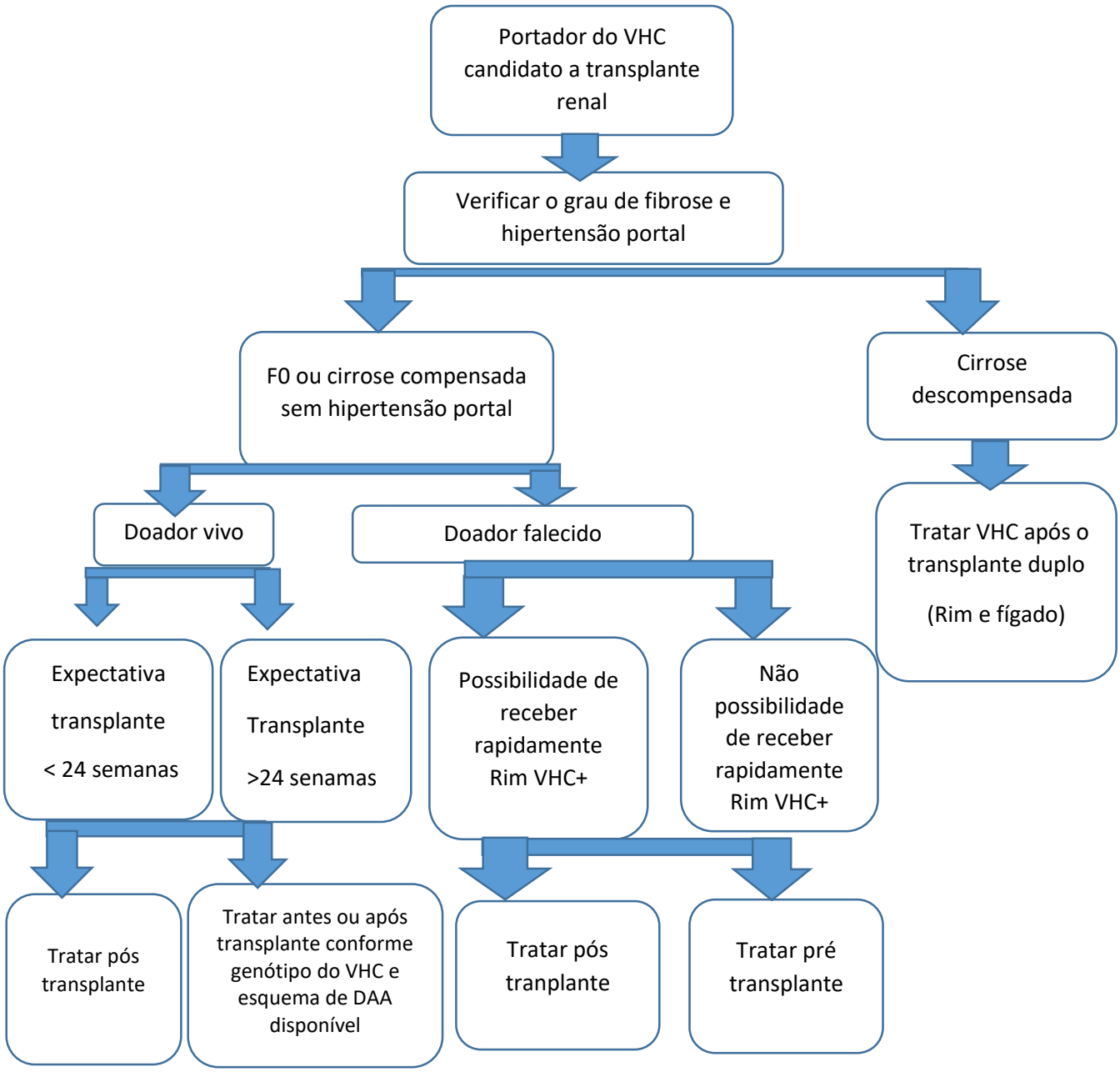
uso de sofosbuvir 400mg em dias alternados ou três vezes na semana alcançou RVS de 88% e não houve perda da função renal.

1.6 Tratamento com DAA em transplantados renais

Estudos em pacientes transplantados renais tratados com diferentes DAA, destacam a obtenção de RVS de 100% (36,37,38), embora o número de pacientes avaliado tenha sido pequeno, entre 15 e 25 pacientes. Os pacientes que alcançaram resposta virológica sustentada antes de realizar transplante renal apresentam melhor sobrevida (39,40,41). Além de não haver risco de reativar o VHC em decorrência do uso de imunossupressores (42,43).

A hepatite C crônica pode ser tratada antes ou após o transplante renal. Para decidir quando tratar é importante saber o genótipo do VHC, grau de fibrose hepática, tempo de espera na lista de transplante e taxa de filtração glomerular. Se o tempo de espera para receber o rim for maior de 24 semanas, pode-se tratar o VHC antes do tranplante. Em centros que transplantam órgãos de portadores de VHC, o potencial receptor precisa assinar um termo que aceita receber o rim com VHC (14) (figura 1).

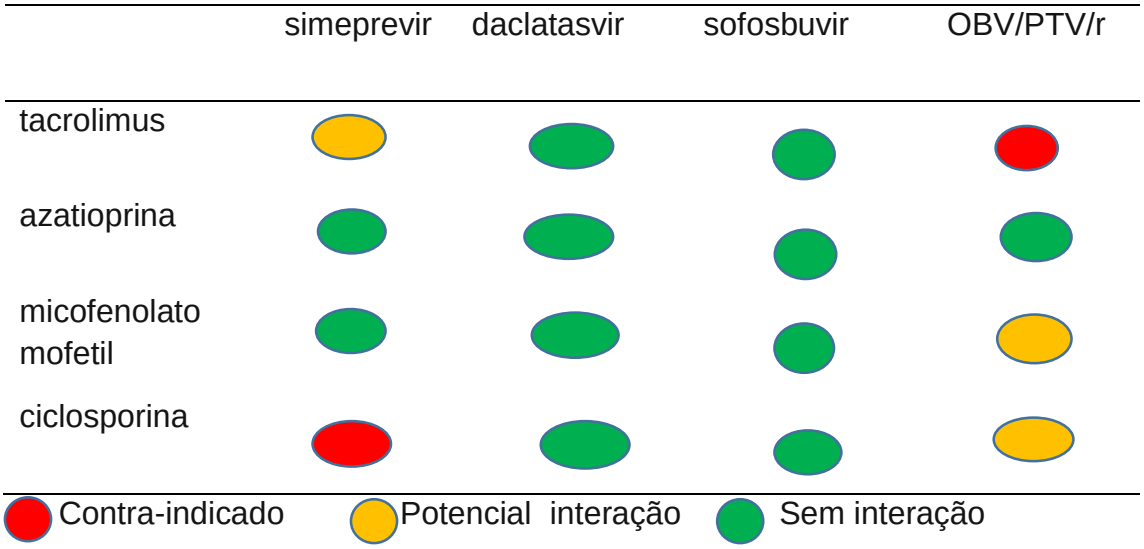
Figura 1: Proposta de estratégia em um candidato a transplante renal infectado pelo vírus da hepatite C (KDIGO 2018)



Adaptado de KDIGO 2018 (14)

É importante ressaltar as interações medicamentosas dos DAA com os imunossupressores, como por exemplo, os inibidores de protease e com inibidores de calcineurina ou alvo de rapamicina em mamíferos (mTOR). O simeprevir tem potencial interação medicamentosa com tacrolimus, sirolimus e everolimus (44). O sofosbuvir e o daclatasvir têm um baixo risco de interação com imunossupressores e têm ação pangenotípica. As nterações medicamentosas de antivirais podem ser analisadas no site da Universidade de Liverpool (figura 2) (44).

Figura 2: Interações medicamentosas entre imunossupressores e DAA



OBV/PT/r: ombistasvir/paritaprevir/ritonavir

Adaptado do site da Universidade de Liverpool (44)

2. JUSTIFICATIVA

Até recentemente, a combinação de PEG- IFN e RBV era a única opção terapêutica para a hepatite C crônica, e os resultados desse tratamento eram limitados devido à baixa eficácia, pouca tolerabilidade e frequentes efeitos colaterais.

Nos pacientes renais crônicos, as taxas de respostas eram ainda mais baixas e os efeitos colaterais maiores. Com o surgimento dos novos antivirais de ação direta (DAA) contra o VHC, o panorama do tratamento da hepatite C sofreu grande modificação, especialmente em pacientes considerados difíceis de tratar.

Uma das principais preocupações que surge em relação ao tratamento com DAA nos pacientes renais crônicos é a segurança quanto à função renal. Além disso, nos pacientes transplantados renais há a questão das interações medicamentosas com os imunossupressores.

Diante do exposto, ensaios clinicos adicionais com os DAA em pacientes com insuficiencia renal grave e após transplante renal são necessários. É de suma importancia traçar o perfil epidemiológico dos pacientes renais crônicos portadores de hepatite C, analisar a evolução clínica, efeitos colaterais e os desfechos, como a RVS.

Assim sendo, os resultados dessa pesquisa poderão trazer uma significativa contribuição sobre a resposta dos pacientes com insuficiência renal crônica e/ou transplantados renais tratados com os DAA contra o vírus da hepatite C, uma vez que esses dados sao escassos na literatura internacional e inexistentes em nosso meio.

3. OBJETIVOS

3.1 GERAL

- Analisar a eficácia do tratamento do vírus da hepatite C com esquemas contendo sofosbuvir nos pacientes portadores de insuficiência renal crônica e/ou transplantados renais.
-

3.2 ESPECÍFICOS

- Tracar o perfil clínico-epidemiológico dos pacientes renais crônicos e portadores do vírus da hepatite C
- Avaliar o impacto do tratamento com esquemas contendo sofosbuvir na função renal

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ARTIGO 1

Elaborado segundo as normas de publicação da revista ARQUIVOS DE GASTROENTEROLOGIA)

Clinical and epidemiological evaluation of patients with chronic hepatitis C virus infection and chronic kidney disease in a reference hospital in Southern Brazil

Título em português: Perfil clínico e epidemiológico dos pacientes com infecção crônica pelo vírus da hepatite C e doença renal crônica em hospital de referência do sul do Brasil

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Conflict of interest: none

Grants: none

Abstract

Context: Patients with chronic kidney diseases (CKD) represent a population at high risk for hepatitis C virus (VHC) infection and have a worse prognosis in the evolution of liver and kidney disease.

Objectives: To describe the clinical and epidemiological profile of chronic renal disease or renal transplant patients with chronic hepatitis C.

Methods: Retrospective observational study in patients with VHC and CKD over 18 years of age. Glomerular filtration rate, presence of renal transplantation, VHC genotype, liver fibrosis degree, comorbidities and use of immunosuppressants The statistical analysis adopted was p of 5% ($p<0.05$)

Results: Seventy patients were analyzed, 42 (60%) were men, the mean age was 52.3 ± 11.0 years,61 (87.1%) were renal transplant patients, with moderate loss of kidney function (mean glomerular filtration rate of 52.3 mL/min/1.71 $m^{2)}$, 32 (59.2%) patients with HCV genotype 1 and non-cirrhotic 58 (82.3%).

Conclusion: Patients with chronic renal disease and chronic VHC infection present moderate loss of renal function and moderate degree of hepatic fibrosis.

Key words: hemodialysis. kidney transplantion. direct-actin antiviral. sofosbuvir. daclatasvir. HCV.

Resumo

Contexto: Pacientes com insuficiência renal crônica (IRC) representam uma população de importante risco de contaminação pelo vírus da Hepatite C (VHC) e apresentam pior prognóstico na evolução da doença hepática e renal.

Objetivos: traçar o perfil clínico e epidemiológico dos pacientes renais crônicos ou transplantados renais portadores de hepatite C crônica.

Métodos: Estudo observacional, retrospectivo, realizado em portadores de VHC e IRC maiores de 18 anos. Foram avaliados taxa de filtração glomerular, presença de transplante renal, genótipo do VHC, grau de fibrose hepática, existência de comorbidades e uso de imunossupressores. Na análise estatística, o nível de significância adotado foi de 5% ($p<0.05\%$).

Resultados: Setenta pacientes foram analisados, houve predomínio de homens 42(60%), média de idade de 52.3±11.0 anos, maioria de transplantados renais 61(87.1%), com perda moderada da função renal (média de Taxa de filtração glomerular 52.3mL/min/1.7 1.73m²), portadores do genótipo 1 do VHC 32 (59.2%) e não cirróticos 58 (82.3%).

Conclusão: Os pacientes com IRC e portadores de VHC crônicos apresentavam moderada perda da função renal e grau moderado de fibrose hepática.

Descritores: hemodiálise, transplante renal, antiviral de ação direta, sofosbuvir, daclatasvir, VHC

Introduction

The prevalence of hepatitis C virus (HCV) infection in patients with end-stage renal disease is clearly higher than in general population. [1] In Brazil, 1.38% of the population is chronically infected with the HCV [2], and among dialysis patients the prevalence of HCV ranges from 4,2% to 8.0%[3].

There are several factors t related to high prevalence rates, such as blood transfusions, injecting drug use, the length of time on hemodialysis, among others [4].

HCV in patients with chronic kidney disease (CKD) is associated with more rapid progression of liver disease, mortality due to complications of cirrhosis, loss of renal graft, and decreased survival. [5]

Management of HCV in these special populations is challenging, because of reduced treatment efficacy, increased side effects, and impaired pharmacokinetics. [6].

The objective of the present study is to evaluate the clinical and epidemiological profile in a cohort of patients with HCV and CKD in a reference centre in Southern Brazil.

Methods

This is a retrospective observational cohort study evaluating outpatient patients with HCV and CKD attended at the Gastroenterology/Hepatology outpatient clinic of Santa Casa de Misericórdia Hospital, Porto Alegre, Brazil. Data were collected from the records of patients between January and December 2017.

The inclusion criteria consisted of patients with HCV aged 18 years or older in any stage of CKD or renal transplantation and not coinfected with human imunodeficiency vírus (HIV).

Clinical characteristics, such as, age, sex, HBV coinfection, HCV genotype, liver fibrosis (by transient hepatic elastography or hepatic biopsy), use of substitutive therapy, renal transplantation were evaluated. The use of immunosuppressive in patients who underwent renal transplantation, and comorbidities were registered. The laboratory data analyzed were creatinine, glomerular filtration rate, aminotransferases, albumin, platelets, prothrombin time. AST/platelet ratio (APRI) and model for end-stage liver disease (MELD) were calculated.

The renal function was assessed by estimated creatinine clearance (CrCl) by the Cockcroft-Gault fórmula: clearence creatinine = [(140 – age) x weight (kg) /creatinine x 72] - men value multiplied by 1.00 and women by 0.85 [(6).] The staging of CKD was performed according to KDIGO 2018[(6)].

The fibrosis was evaluated by transient hepatic elastography (THE) when available or liver biopsy when there was a clinical indication for this procedure.

Chronic infection was defined as the persistence of HCV-RNA for a period of at least six months. HCV viral load was evaluated by polymerase chain reaction (PCR) - Real-time using the Extraction and Amplification Method: COBAS® AmpliPrep / COBAS® TaqMan® HCV Quantitative Test, v2.0 (Roche).

Variables with symmetrical distribution were described by mean and standard deviation and compared by Student's t-test for independent variables. Variables with asymmetric distribution were described by the median and the

interquartile range (25^{th} and 75^{th} percentiles) and compared by the Mann-Whitney test. All statistical analyzes were performed using SPSS software version 23 (IBM, Armonk, NY, USA). The assumed level of significance was 5%.

The present study was approved by the local Ethics Committee under number 1838479, and is in accordance with the Resolution 466/2012 of the National Health Council (Brazil).

Results

Seventy patients with VHC and CKD were evaluated. The mean age was 52 ± 11 years (26 to 81 years), and predominance of 42 (60%) males. Sixty one (87.1%) patients have been previously submitted to renal transplantation, 8 (11.4%) were on hemodialysis and only 1 (1.42%) was a patient with CKD on conservative treatment.

Considering the stages of chronic renal failure (CKD), 6 (8.6%) patients were in stage I, 17 (24.2%) in stage II, 23 (32.8%) in stage III, 13 (32.8%) in stage IV and 11(15.8%) in stage V.

Regarding the renal function, the mean creatinine level was 2.4 ± 2.7 mg/dL and the mean GFR was 52.3 ± 29.7 mL/min.

The HCV genotype was evaluated in 54 (77.1%) patients. Genotype 1 was the most prevalent (59.3%), followed by genotypes 3 (35.2%) and 2 (3.7%). The sub genotype 1a was the most prevalent (38.9%). Coinfection of different genotypes (3 and 4) was identified in one patient. The majority of the patients (n=58; 82.9%) were not previously treated for HCV.

The most common comorbidities were systemic arterial hypertension in 27 (38.6%), diabetes melitus (DM) in 14 (20%) and cardiac arrhythmia in 2 (2.9%).

Four (5.7%) patients were coinfected with the hepatitis B virus and most were non-cirrhotic 58 (82.9%).

To evaluate liver fibrosis, 14 (20%) patients performed liver biopsy and 25 (35.7%) by THE.

Fibrosis was classified by THE as F0-F1 in 09 (36%), F2 in 07 (28%), F3 in 5 (20%) and F4 in 04 (16 %) patients.

Twelve (17.1%) patients were cirrhotic, diagnosed by clinical manifestations or complications (ascites, spontaneous bacterial peritonitis, esophageal varices or hepatic encephalopathy) and by THE in 4 (16%) patients. Among the cirrhotic patients, Child-Pugh A predominated (90%).The data can be observed in table 1.

The analysis of the hepatic profile showed altered aminotransferases in 25/65 (38.4%) patients, serum albumin greater than 3.5 mg / dL in 49/51 (96%) patients, 15/68 (22%) had platelets below 150 x 10^3/µL, 7/70 (10%) hemoglobin <12mg/dL, and all patients had total bilirubin below 2mg/dL. The mean AST/platelet (APRI) score was 1.04 ± 1.37. In cirrhotics, the mean model for end-stage liver disease (MELD) was 15.5 ± 4.4.

Mean creatinine of 2.4 ± 2.7mg/dl and glomerular filtration rate of 52.3 mL/min/1.71 $m^{2)}$. The data presented can be seen in table 2.

When evaluated the patients who underwent renal transplantation, the most commonly used immunosuppressive regimen was the combination of Prednisone, Mycophenolate and Tacrolimus (n=25; 41%).

Discussion

Hepatitis C virus (HCV) infection is most commonly found in patients with CKD undergoing substitutive therapy. It is believed that viral transmission can

occur due to several factors such as surgeries, transfusions and many procedures to which hemodialysis patients are routinely submitted. In Brazil, after the implementation of screening tests in blood banks in 1993, there was a decrease in the transmission of this virus during transfusions. There is an association of the time (in years) the patient is on dialysis and the risk of HCV infection. [7]

The Kidney Disease Guideline: *Improving Global Outcomes* (KDIGO 2018) [6] suggests to perform hepatitis C screening in patients on dialysis with an anti-HCV testing when entering the hemodialysis or peritoneal dialysis program. The surveillance for early diagnosis with new anti-HCV should be maintained every 6 months. If the patient presents a positive anti-HCV and negative viral load, keep monitoring with viral load every 6 months. In addition, the ALT should be monitored monthly, and if there is any modification, a new anti-HCV test must be performed again.

Several authors reported false-negative results on anti-HCV antibody testing in patients undergoing hemodialysis due to immunosuppression. This highlights the importance of performing the viral load, which is the sensitive and specific diagnostic method for hepatitis C infection [6-9].

ALT levels do not change frequently in patients with HCV on hemodialysis, suggesting that aminotransferases are not good predictors of hepatocellular injury for these patients, since there is enzymatic inhibition by uremic toxins, pyridoxine deficiency (aminotransferase cofactor), loss of enzymes in dialysis and interference of other dialysable substances in the dosage of aminotransferases. The mean ALT level found in the present study was 55 IU/L,

a higher value than the observed by Fabrizi et al (26.5 IU/L) when evaluated the aminotransferases level and viral load. [10]

The distribution of the HCV genotypes in this study was similar to that observed in the study by Campiotto [11] carried out in different locations in Brazil and Vidales-Braz [12] performed in southern Brazil. Genotype 1 was the most prevalent (45.7%).

Four (5.7%) patients were coinfected with the hepatitis B virus. Treatment of hepatitis C with new DAA may represent a risk for reactivation of hepatitis B virus in co-infected patients with HCV. A systematic review and meta-analysis found 17 studies involving 1621 patients, 242 with HBV and 1.379 with resolved hepatitis B (HbsAg-negative but anti- HBcAb-positive). All were treated with different regimens containing DAA against HCV. The reacivation of VHB was observed in 24% (IC95% 19-30) in patients with chronic HBV infection and 1.4% (0.8-2.4) in those with HBV infection resolved [13].

Staging of hepatic fibrosis through biopsy or non-invasive methods is recommended in all renal transplant candidates, although treatment can be performed independently of this evaluation [14]. THE have similar accuracy to liver biopsy in CKD patients compared to the general population, and the KDIGO guideline recommends initial evaluation of hepatic fibrosis by non-invasive methods. The objectives of the analysis of the degree of fibrosis is to decide the time of treatment with DAA and to diagnose cirrhosis. In addition to considering isolated kidney transplantation for compensated cirrhosis and conjugated liver transplantation in decompensated cirrhotics. In addition to the fibrosis grade, it is to decide to treat before or after renal transplantation, it is important to know the expected time for transplantation, genotype and GFR. For example, a patient with

F0 and expectation of receiving transplant before twenty-five weeks can treat HCV post- treatment .[14].

Hepatitis C virus infection may be also responsible for worsening renal function and other extrahepatic manifestations, such as lymphoma, cryoglobulinemia, and atherosclerosis. Therefore, it is recommended to monitor the renal function of all those infected by VHC. [14] . The study demonstrated that patients with HCV had a 27% increased risk of CKD compared with patients without HCV. This study also revealed that VHC-positive patients experienced a 2-fold higher risk of membranoproliferative glomerulonephritis (MPGN) and a nearly 17-fold higher risk of cryoglobulinemia. Effective antiviral treatments have been shown to reduce risk of CKD by 30%[15].

HCV infection has a negative impact on the survival of post-renal transplant patients due to the increased risk of graft loss due to rejection and glomerular disease induced by the virus, infections, post-transplantation diabetes, cancer and rapid progression of liver fibrosis. [15] Although HCV eradication is of prominent importance, renal transplant recipients have always represented a special population of difficult treatment. Interferon-based therapies were associated with low rates of sustained virological response (SVR 17-38%) and high risk of graft dysfunction (51%), being contraindicated in those who undergone to kidney transplantation. [16] Currently, the use of DAA has been an important step in the treatment of HCV infection due to SVR ranging from 60% to 100% according to genotype and degree of hepatic dysfunction. [17,18,19] There are few studies on the use of DAA in patients with CKD or kidney transplant recipients, but with encouraging results. [20,21,22,23]. In the present study, more than half of the cohort is waiting the use of DAA.

Most of the patients in this study were immunosuppressed by tacrolimus. To know the drug interactions of DAA is of fundamental importance, particularly the interaction between protease inhibitors and calcineurin inhibitors or mammalian target of rapamycin (mTOR) inibitors. [24]

Conclusion:

In conclusion, this study evaluated a representative sample of chronic kidney diseases patients in a reference center in the southern region of Brazil. The majority of patients were non-cirrhotic, kidney transplant recipients, HCV, genotype type 1, used immunosuppressants, had comorbidities and potential drug interactions, therefore they are a special population.

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Table 1: Clinical characteristics of patients with VHC and CKD (n=70)

Age; years	52.3 ± 11.0
Sex, Male	42 (60)
VHB coinfection	04 (5.7)
Kidney transplant recipientes	61 (87.1)
CKD staging (Crcl; mL/min)	
1 (Crcl >90)	6 (8.6)
2 (Crcl 60-89)	17(24.2)
3 (Crcl 30-59)	23 (32.8)
4 (Crcl 15-29)	13 (18.5)
5 (Crcl <15 or Hemodyalisis)	11 (15.8)
VHC Genotypes	54 (77.1)
1 a	21 (38.9)
1 b	11 (20.4)
2	02 (3.7)
3	19 (35.2)
3+4	01 (1.85)
Comorbidities	59 (84.2)
Systemic arterial hypertension	27 (38.6)
Diabetes mellitus	14 (20.0)
Arrhythmia	02 (2.9)
Cirrhosis	12 (17.1)
CTP A	11 (91.6)
CTP B	01 (0.8)
CTP C	0 (0)

Liver biopsy	14 (20.0)
F0	03 (4.3)
F1	04 (5.7)
F2	06 (8.6)
F3	01 (1.4)
F4	0 (0)
Transient hepatic elastography	25 (35.7)
F0	04 (16.0)
F1	05 (20.0)
F2	07 (28.0)
F3	05 (20.0)
F4	04 (16.0)

CKD = chronic kidney disease; CTP = Child Tourcotte- Pugh escore; CrCl: Creatinine clearance; HBV: hepatitis B virus; HCV: hepatitis C virus;

Table 2: Laboratorial characteristics of patients with VHC and CKD

Variable (n)	Mean ± standard deviation
Creatinine; mg/dl (70)	2.4 ± 2.7
GFR; mL/min/1.73m² (70)	52.3 ± 29.7
AST; U/L (65)	48.2 ± 33.5
ALT; U/L (68)	55.0± 42.2
Albumin; g/dL (51)	4.2 ± 0.4
Platelets; x 10^3/µL (68)	175.7 ± 64.8
TB; mg/dL (59)	0.7 ± 0.4
HB; g/dL (70)	13.3 ± 1.8
APRI score (64)	1.04 ± 1.37
MELD (12)	15.5 ± 4.4

GFR = glomerular filtration rate AST: aspartate aminotransferase; ALT: alanine aminotransferase; TB: total bilirubin; HB: hemoglobin; APRI score: AST/platelet ratio; MELD: model for end-stage liver disease

10. ARTIGO 2:

(Elaborado segundo as normas de publicação da revista ANNALS OF HEPATOLOGY)

Treatment of chronic hepatitis C in patients with chronic renal disease with sofosbuvir-basead regimes

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Conflict of interest: none

Grants: none

- Abreviations

- HCV :virus da hepatite C
- HBV :virus da hepatite B
- DAA: direct-acting antiviral
- CKD: chronic kidney disease
- SVR: sustained virological resposnse
- GFR: glomerular filtration rate
- SOF: sofosbuvir
- KDIGO: Kidney Disease Improving Global Outocomes
- PCR: polymerase chain reaction
- ANOVA: analysis of variance
- GESF: Focal segmental glomerulosclerosis
- DM: diabetes mellitus
- SAH: systemic arterial hypertension
- THE: transient hepatic elastography
- CTP: Child-Turcotte-Pugh
- Mtor: mammalian target of rapamycin
- NS3/4A: nonstructural protein 3/4A
- NS5A: nonstructural protein 5A
- NS5B: nonstructural protein 5B
- ALT: alanine aminotransferase
- CrCl: creatinine clearance
- AZA: azathioprine
- CYA: cyclosporin

- **FK:** tracolimus
- **MMF:** mycophenolate mofetil
- **Com:** comorbidities
- **Gen:** genotype
- **Cr:** creatinine
- **SAH:** systemic arterial hypertension
- **DM:** diabetes mellitus
- **CHF:** congestive heart failure
- **AF:** atrial fibrillation

Abstract

INTRODUCTION AND AIM: The advent of direct-acting antivirals (DAA) dramatically changed the treatment of hepatitis C virus (HCV), including those with chronic kidney disease (CKD). The aim of the present study was to analyze the effectiveness and the safety of Sofosbuvir-based regimens to treat patients with HCV and CKD.

MATERIAL AND METHODS: A retrospective, observational study in patients with chronic HCV and CKD treated with sofosbuvir-based regimens. Liver fibrosis, comorbidities, HCV genotype and sustained virological response (SVR) at 12th week post-treatment were evaluated. Renal function was accessed by serum creatinine and estimated glomerular filtration rate (GFR). The assumed level of significance was 5%.

RESULTS: Thirty-five patients being 33 (94.3%) treated with sofosbuvir and daclatasvir and 2 (5.7%) with sofosbuvir and ribavirina were analyzed, 19 (54.3%) were women, mean age of 52.1±10.9 years, 32 (91.4%) were already renal transplanted and 3 (8.6%) were on hemodialysis. Coinfection with hepatitis B virus (HBV) was found in 2 patients (5.7%), with reactivation of HBV in one. The mean GFR was 65.8±28.6 and 63.7±28.3 mL/min pre- and post-treatment respectively ($p>0.05$). There was no difference between the CKD levels throughout the follow-up ($p=0.459$). The SVR by intention to treat was 88.6% and per protocol 96.9%. Treatment was interrupted in 1 (2.85%) patient due to anemia and in 2 (5.7%) due to loss of renal function. The was no death during the period.

CONCLUSION: Sofosbuvir is effective in patients with CKD, but should be monitored for eventual loss of renal function.

Key words: hemodialysis; kidney transplantion; direct-acting antiviral; sofosbuvir; daclatasvir; HCV.

The prevalence of hepatitis C virus (HCV) infection in patients with end-stage renal disease is clearly higher than the observed in the general population (1) In Brazil, 1.38% of the population is infected with HCV (2) and in patients on dialysis, the prevalence of this infection ranges from 4.2% to 8% depending on the renal replacement therapy center (3). HCV infection in patients with chronic kidney disease (CKD) is associated with a more rapid progression of liver disease, increased mortality due to complications of cirrhosis, loss of renal graft and glomerulonephritis, thus contributing to a worse prognosis in these patients (4). Despite the relationship between HCV and the progression of CKD the vast majority of patients with CKD remained untreated, because they were historically a difficult to treat population due to the frequent adverse effects associated with medications used to treat HCV (5,6). In addition to the complexity of the treatment, the use of Interferon in renal transplant recipients may be associated with a high risk of graft rejection (15% to 100%) and is contraindicated in this set (7).

The advent of direct-acting antivirals (DAA) dramatically changed the treatment of HCV including the special population of patients with CKD. In 2015, the use of sofosbuvir (SOF) based regimens was approved in Brazil (8). Renal transplant patients and patients on hemodialysis have been treated with DAA since then, but the importance of individualizing the treatment due to the risk renal disfunction was also emphasized.

The objective of the present study was to analyze the effectiveness and the safety of sofosbuvir-based regimens to treat patients with CKD.

METHODS

A retrospective, observational study was performed in all patients cronically infected with HCV and CKD at various stages treated with SOF-based regimens at the Gastroenterology/Hepatology outpatient clinic of the Santa Casa Hospital, Porto Alegre, Brazil from June 2016 to March 2018.

The age, gender, liver fibrosis, comorbidities, HCV genotype and sustained virological response (SVR) at 12th week post-treatment were evaluated.

Renal function was accessed by serum creatinine and GFR calculated using the Cockroff-Gault formula before, after treatment and 3 months after the end of treatment (5). Chronic kidney disease was classified at different stages according to criteria established by Kidney Disease Improving Global Outocomes (KDIGO) (5). Kidney transplantation prior to treatment and the use of immunosuppressants were also registered.

Chronic HCV infection was defined as the persistence of VHC-RNA for a period of at least six months. Molecular diagnosis VHC were performed by polymerase chain reaction (PCR) - Real-time using the Extraction and Amplification Method: COBAS® AmpliPrep / COBAS® TaqMan® HCV Quantitative Test, v2.0 (Roche).

Patients were considered to have cirrhosis based on clinical, image, laboratory or histologic parameters (METAVIR score) (9).

Treatment with DAA was performed according to the Brazilian Public Health system (2015) (8), which recommended that patients with CKD and kidney transplant patients should be treated with a non-interferon-alpha regimen and, if possible, without ribavirin.

In the statistical analysis, the quantitative variables were described by mean and standard deviation (if normal distribution) or median and interquartile range (if asymmetric distribution). The normality of the continuous variables was evaluated by the Shapiro-Wilk test. Categorical variables were described by absolute and relative frequencies. To compare means before and after treatment, the paired t-student test was applied. In case of asymmetry, the Wilcoxon test was used. For the categorical variables, the McNemar test was applied. To compare means between the three moments, the analysis of variance (ANOVA) for repeated measures was applied. In case of asymmetry or ordinal variables, the Friedman test was used. The association between numerical and ordinal variables was evaluated by the Spearman correlation coefficient. The significance level adopted was 5% ($p < 0.05$) and the analyzes were performed in the SPSS program version 21.0.

The present study was approved by the Research Ethics of local Committee (number 1838479).

RESULTS

Thirty-five patients were analyzed. There was a light predominance of females 19 (54.3%), the mean age was 52.1 ± 10.1 years (34 to 70 years), 32 (91.4%) were previously submitted to renal transplants and 3 (8.6%) patients were on hemodialysis (Table 1).

Considering the stages of chronic renal failure disease (CKD), 16 (45.7%) were stage III or worse. Regarding the etiology of renal failure, 24 (68.5%) had no diagnosis, and systemic lupus erythomatous was found in 3 (8.57%) patients. Focal segmental glomerulosclerosis (GESF), diabetes mellitus (DM), systemic

arterial hypertension (SAH) , polycystic kidney disease, Alport syndrome, chronic pyelonephritis and Bor syndrome were responsible for the etiology in a few patients (8; 22.8%). HCV genotype 1 was the most prevalent (22; 62.8%) (Table 1).

Coinfection with hepatitis B virus (HBV) was found in 2 patients (5.7%). There it was observed the reactivation of HBV in one of these, immediatly post-treatment of HCV in was a renal transplant patient, genotype 1 patient, using tenofovir since 2012, with HBV viral load undetectable pre-treatment. The patient presented SVR after HCV treatment, and after HBV reactivation, entecavir was associated with tenofovir.

In the evaluation of liver fibrosis, no patient underwent liver biopsy. Transient hepatic elastography (THE) was performed in 12 (34.2%) patients, showing absence or mild/significant fibrosis (F0-F1-F2) in 7 (58.3%) and advanced fibrosis (F3-F4) in 5 (41.7%) patients. Cirrhosis was diagnosed by THE in 4 (11.4%) patients, and by clinical presentation (portal hypertension with ascites and esophageal varices) in 4 (11.4%). Among the 8 cirrhotics, 5 (14.2%) were Child-Turcotte-Pugh (CTP) A and 3 (8.6%) CTP B (Table 1).

The prevalent comorbidities were systemic arterial hypertension in 18 (51.4) patients, diabetes mellitus in 11 (31.4%), heart failure in 3 (8.6%) and cardiac arrhythmia in 4 (11.4%) (Table1).

Of the 35 patients who underwent HCV treatment, 33 (94.2%) were treated with sofosbuvir and daclatasvir, of whom 8 (24.2%) received ribavirin. The 2 (5.7 %) patients with HCV genotype 2 were treated with sofosbuvir and ribavirin (Table2).

Full dose of sofosbuvir was used in 33 (94.2%) patients, and half dose (1 tablet on alternate days) in 2 (5.7%) patients.

Thirty-two (91.4%) patients were receiving immunosuppressants because they were kidney transplant recipients. Immunosuppressive regimens were not modified during HCV treatment. There was a predominance of prednisone associated with mycophenolate mofetil and tacrolimus in 15 (42.9%) patients (Table 3).

The treatment was suspended in 3 (8.6%) patients, in 1 (2.8%) due to anemia and 2 (5.8%) due to a significant loss of renal function. The 3 patients who stopped treatment were cirrhotic, and the one who had anemia was on hemodialysis.

SVR was evaluated in 32 patients who completed the treatment, and 31 (88.6%) achieved SVR 12 in an intention to treat analysis; per protocol 96.9%. Only 1 (2.8%) presented HCV recurrence after treatment.

When the median creatinine and mean GFR were analyzed, there was no statistically significant difference before and after treatment with bases sofosbuvir (Table 4). Creatinine improvement was observed in 19 (54.3%) patients, and the worsening in 12 (34.3%) patients, though only 2 (5.7%) progressed to a more advanced stage of CKD. The remaining 4 (11.4%) patients did not present any difference in renal function before and after treatment. (Table 5).

DISCUSSION

In the present study, a series of cases of patients with chronic renal disease and HCV were treated with the new DAA, successfully achieving SVR and there is no dysfunction. Most of the patients were renal transplant patients, non-cirrhotic

patients with HCV genotype 1, and the most commonly used treatment regimen was the association of sofosbuvir and daclatasvir for 12 weeks.

Hepatitis C virus often has a negative impact on the survival of post-renal transplant patients due to the increased risk of graft loss due to rejection and disease infection, post-transplant diabetes, cancer and rapid progression of liver fibrosis (10).

Although eradication of HCV is of paramount importance, renal transplant recipients have always represented a special difficult to treat population. Currently, the use of DAA has been an important step in the treatment of HCV infection due to rates of SVR ranging from 60% to 100% according to genotype and degree of hepatic dysfunction (11).

Manys studies in the literature that evaluate the use of DAA in chronic kidney disease presented with encouraging results. Desnoyer A et al (12) observed that sofosbuvir was well tolerated in 13 dialysis patients. However, SVR12 was 100% in patients who used Sofosbuvir full dose and 60% in those who received three times a week. Saxena et al (13) observed, in Saxena study (n = 19, being 5 on hemodialysis), no difference in the SVR regardless of renal function. However, patients with GFR <30 mL/min experienced more anemia and worsened renal function after using sofosbuvir (13). Studies on kidney transplant recipients treated with DAA stand out with 100% SVR12 (14,15,16). This study confirms that sofosbuvir-based therapies are effective in patients with CKD. In this series of 35 cases, the SVR12 was reached in 31 (88.6%) patients. Only one patient (2.8%) developed HCV recurrence after treatment; he was genotype 1A, under

hemodialysis, presented fibrosis F1 evaluated by transient hepatic elastography and was treated with sofosbuvir, daclastavir and ribavirin for 12 weeks.

Treatment of hepatitis C with new DAA may represent a risk for reactivation of hepatitis B virus in co-infected patients with HCV. A systematic review and meta-analysis found 17 studies involving 1621 patients, 242 with HBV and 1.379 with resolved hepatitis B (HBsAg-negative and anti- HBc-positive). All were treated with different regimens containing DAA against VHC The reacivation of HBV was observed in 24% (IC95% 19-30%) in patients with chronic HBV infection and 1.4% (0.8-2.4%) in those with resolved HBV infection (17). In the present study, 2 (5.7%) patients were HBsAg positive, and one reactivated HBV during use de DAA.

To know the drug interactions of DAA is of fundamental importance, particularly the interaction between protease inhibitors and calcineurin inhibitors or mammalian target of rapamycin (mTOR) inibitor, Simeprevir, a second-generation antiviral that inhibits the protease coded by the HCV NS3/4A region, has potential drug interaction with tacrolimus, sirolimus and everolimus (18). Sofosbuvir (polymerase inhibitor encoded by the HCV NS5B region) and daclatasvir (HCV NS5A region-encoded polymerase inhibitor) have a low risk of interaction with immunosuppressants and have pangenotypic action. In this study, the vast majority of patients were renal transplant patients (33; 94.3%).

All patients were treated with sofosbuvir based regimes. Renal transplant patients were using immunosuppressants, 8 (25.0%) used schedules with ciclosporin, and 17 (48.5%) with tacrolimus. There was no need for more frequent control of the levels of immunosuppression due to the lack of drug interaction with these DAA.

This study showed that treatment with sofosbuvir was well tolerated in chronic renal patients, but 3 (8.6%) patients discontinued therapy. The two patients worsening renal function were cirrhotic Child-Turcotte-Pugh B, renal transplanted, in the advanced stages of CKD stage 3 (GFR 41mL/min) and stage 4 (GFR 27 mL/min). The other patient who discontinued treatment for symptomatic anemia (hemoglobin drop) was cirrhotic on hemodialysis using sofosbuvir, daclatasvir and ribavirin.

There was no statistically significant difference between creatinine levels and glomerular filtration rate before, at the end after three months of treatment.

In conclusion, this study suggests that treatment HCV in patients with CKD is safe and effetive with potential benefit in renal function treated with DAA and obtaining SVR. However, these should be monitoring for GFR decline. On the other side, there was a little improvement in renal function in the vast majority of patients after treatment. Future studies are needed to determine predictors of renal recovery with VHC eradication and to confirm long-term effects of HCV eradication on renal function.

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Table 1: Clinical characteristics of patients with HCV and CKD (n=35)

Clinical characteristics	
Age; years; m ± DP [range]	52.1 ± 10,9 [34 – 70]
Sex,female; n (%)	19 (54.3)
VHB coinfection; n (%)	02 (5.7)
Kidney transplant recipientes; n (%)	32 (91.4)
CKD staging (Crcl; mL/min); n (%)	
1 (Crcl> 90)	06 (17.1%)
2 (Crcl 89-60)	13 (34.2%)
3 (Crcl 59-30)	12 (37.1%)
4 (Crcl 29-15)	01 (2.9%)
5 (Crcl <15 ou hemodialysis)	03 (8.6%)
VHC Genotypes; n (%)	
1 A	16 (45,7)
1 B	06 (17.1)
2	03 (8.6)
3	09 (25.7)
3+4	01 (2.9)
Comorbidities	
Systemic arterial hypertension	18 (51.4)
Diabetes mellitus	11 (31.4)
Cardiac failure	03 (8.6)
Arrhythmia	04 (11.4)
Cirrhosis; n (%)	08 (22.8)

CTP A	04(11.4)
CTP B	04 (11.4)
CTP C	00 (0)
Hepatic elastography; n (%)	12 (34.3)
F0	03 (8.6)
F1	03 (8.6)
F2	01 (2.9)
F3	01 (2.9)
F4	04 (11.4)

CDK = chronic kidney disease; CTP = Child Turcotte- Pugh escore; CrCl: creatinine clearance; HBV: hepatitis B virus; HCV: hepatitis C vírus.

Table 2: Medications used in the treatment of patients with HCV and CKD (n=35)

Medications	N (%)
sofosbuvir + daclatasvir 12 weeks	27 (77.1)
sofosbuvir + daclatasvir + ribavirin 12 weeks	03 (8.6)
sofosbuvir + daclatasvir + ribavirin 24weeks	03 (8.6)
sofosbuvir + ribavirin 12 weeks	02 (5.7)

Table 3: Imunosuppressants in CKD patients submitted to renal transplantation (n=32)

Imunosuppressants	n (%)
prednisone, MMF and FK	15 (42.9)
prednisone and MMF	06 (17.1)
prednisone, MMF and CYA	04 (11.4)
prednisone AZA and CYA	03 (8.6)
prednisone and FK	02 (5.7)
prednisone + CYA+ Sirolimo	02 (5.7)

AZA: azathioprine; CYA: cyclosporin; FK: tracolimus; MMF: mycophenolate mofetil

Table 4 : Comparison of creatinine and glomerular filtration rate (GFR) pre, post and three months after treatment.

Variables	Pre	Post	3 months after treatment	p
Creatinine (mg/dL); Median (P25 – P75)	1.27 (0.94 – 1.57)	1.23 (0.92 – 1.70)	1.28 (0.92-1.92)	0.573*
GFR (mL/minuto); Median ± SD	65.8 ± 28,6	63.7 ± 28,3	64.4 ± 29,8	0.241**

Friedman test; ** analysis of variance (ANOVA) for repeated measures,GFR : glomerular filtration rate; SD = standard deviation

Table 5 - Clinical characteristics of the patients included in the study (n=35)

Patient	Gen	Com	Cr pre	Cr post	▲Cr	GFR pre	GFR post	▲ GFR	Cr 3m post	GFR 3 m post
1*	**3+ 4**	**DM**	**1.17**	**1.22**	**0.05**	**59**	**58**	**- 1**	**1.24**	**66**
2	3	SAH	0.75	0.73	- 0.02	100	100	0	0.73	100
3*	**1**	**DM**	**1.57**	**2.06**	**0.49**	**47**	**22**	**- 25**	**1.9**	**33**
4*	**1ª**	**SAH**	**0.91**	**1.08**	**0.17**	**88**	**80**	**- 0.8**	**0.99**	**88**
5	3	DM	1.17	1.05	- 0.12	85	87	2	1.09	85
6	1ª	-	0.72	0.72	0	100	100	0	0.61	100
7*	**1ª**	**SAH**	**1.71**	**2.19**	**0.48**	**47**	**37**	**- 10**	**1.93**	**41**
8*	**1ª**	**DM**	**2.49**	**3.05**	**0.56**	**27**	**25**	**- 2**	**2.42**	**28**
9	3	SAH	0.71	0.6	- 0.11	144	123	- 21	0.6	130
10*	**1b**	**SAH/AF**	**1.35**	**1.41**	**0.06**	**69**	**66**	**- 0.3**	**1.43**	**65**
11	1	SAH	1.27	1.21	- 0.06	70	71	1	1.28	70
12*	**1**	**SAH**	**1.4**	**1.7**	**0.22**	**51**	**45**	**6**	**1.92**	**39**
13	3	DM	1.0	0.87	- 0.13	73	84	11	0.92	79
14	3	SAH	4.9	4.9	0	14	14	0	5.4	12
15	2	DM	1.54	1.29	- 0.25	52	51	- 1	1.16	69
16*	**3**	**DM**	**1.91**	**2.28**	**0.37**	**41**	**29**	**- 12**	**2.34**	**33**
17	1	SAH	0.94	0.91	- 0.03	82	85	3	0.94	82
18	1	DM	1.28	1.45	0.17	58	52	- 6	1.67	46

19	1	SAH/DM/ CHF	1.24	1.22	- 0.1	70	71	1	1.28	68
20	2	DM	11	11	0	7	7	0	6.7	12
21*	**1b**	**SAH**	**1.18**	**1.23**	**0.05**	**58.4**	**59.3**	**0.01**	**1.21**	**57**
22	1b	AF	1.61	1.58	- 0.03	79	80	1	1.61	61
23	1b	SAH/DM	2.57	2.22	- 0.35	51	59	- 8	2.57	60
24*	**1b**	**DM**	**1.41**	**1.68**	**0.27**	**51**	**43**	**- 8**	**2.78**	**26**
25	3	SAH/DM	0.78	0.74	- 0.04	89	87	- 2	0.78	89
26	1	SAH/DM	1.38	1.3	- 0.08	53	56	3	1.36	54
27	1	-	7.75	5.88	- 1.87	8	11	3	5.99	11
28	1	DM	0.85	0.83	- 0.02	66	66	0	0.88	64
29	1b	SAH	1.57	1.56	- 0.01	62	63	1	1.77	55
30	1	SAH	0.79	0.79	0	100	100	0	0.69	115
31	1	-	0.96	0.92	- 0.04	66	69	3	0.92	69
32	2	SAH	0.96	0.95	- 0.01	86	87	1	0.94	88
33*	**3**	**SAH**	**0.97**	**1.05**	**0.08**	**94**	**87**	**- 7**	**0.95**	**96**
34	3	SAH	1.44	1.26	- 0.18	54	62	8	1.43	55
35*	**1**	**SAH/DM**	**0.92**	**0.97**	**0.05**	**103**	**97**	**- 6**	**0.87**	**109**

Com = comorbidities; gen = genotype; cr = creatinine; GFR = glomerular filtration rate; SAH = systemic arterial hypertension; DM = diabetes mellitus; CHF = congestive heart failure; AF = atrial fibrillation;

* Patients with worsening renal function

7. CONCLUSÃO

1. O tratamento com esquemas à base de sofosbuvir em pacientes renais crônicos portadores de hepatite C crônica é eficaz, com RVS de 96,9% por protocolo e 88,6% por intenção de tratamento.
2. A maioria dos pacientes avaliados era composta por não cirróticos, transplantados renais, portadores do genótipo 1 do VHC, em uso de imunossupressores, com comorbidades e potenciais interações medicamentosas, compondo uma população especial de doentes a serem tratados.
3. Apesar de ter havido melhora na taxa de filtração glomerular após o uso de DAA na maioria dos pacientes, deve haver monitoração da função renal pelo risco de eventual declínio da mesma.
4. Há necessidade de futuros estudos para determinar preditores de recuperação da função renal após a erradicação do VHC e confirmar a longo prazo os efeitos do tratamento da infecção crônica pelo VHC nos pacientes renais crônicos.