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Skuteczność i bezpieczeństwo leczenia przewlekłego WZW typu C w schemacie bezinterferonowym u pacjentów z przewlekłą chorobą nerek

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne

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Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych
Warszawskiego Uniwersytetu Medycznego

Warszawa, 2023 r.

Słowa kluczowe: terapia bezinterferonowa, leki o bezpośrednim działaniu przeciwwirusowym, przewlekłe wirusowe zapalenie wątroby typu C, przewlekła choroba nerek

Keywords: interferon-free treatment, direct-acting antivirals, chronic hepatitis C, chronic kidney disease

Mieszkowi i Krzesiowi...

Wykaz publikacji stanowiących pracę doktorską

1. Czarnecka, P., Czarnecka, K., Tronina, O., Baczkowska, T., & Durlik, M. **Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?**
   Renal Failure, 2022 Punkty IF: 3,000 Punkty MEiN: 40
   Indywiduany udzial procenotwy w przygotowaniu pracy: **90%**

2. Czarnecka, P., Czarnecka, K., Tronina, O., Baczkowska, T., Zarychta-Wisniewska, W., & Durlik, M..
   Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross- Sectional Survey.
   Journal of Clinical Medicine, 2023 Punkty IF: 3,900 Punkty MEiN: 140
   Indywiduany udzial procenotwy w przygotowaniu pracy: **95%**

3. Czarnecka, P., Czarnecka, K., Tronina, O., Bączkowska, T., Wyczałkowska-Tomasik, A., Durlik, M., & Czerwinska, K..
   Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study.
   Journal of Clinical Medicine, 2023 Punkty IF: 3,900 Punkty MEiN: 140.
   Indywiduany udzial procenotwy w przygotowaniu pracy: **90%**

Sumaryczny Impact Factor: 10,8 pkt.
Sumaryczna punktacja MniSW: 320 pkt.

Spis treści

Wykaz stosowanych skrótów 6

Wstęp 6

Założenia i cel pracy 15

Streszczenie w języku polskim 16

Publikacja 1: Utilization of HCV viremic donors in kidney transplantation: a chance or a threat? 16

Publikacja 2: Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey 17

Publikacja 3: Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. 19

Streszczenie w języku angielskim 20

Publication 1: Utilization of HCV viremic donors in kidney transplantation: a chance or a threat? 20

Publication 2: Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey 21

Publication 3: Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. 22

Podsumowanie i wnioski 23

Kopie opublikowanych prac 25

Opinia Komisji Bioetycznej lub Etycznej 73

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie 75

Wykaz stosowanych skrótów

AASLD - *American Association for the Study of Liver Disease;* **ALT**- *alanine aminotransferase*, aminotransferaza alaninowa; **AST-** *aspartate aminotransferase*, aminotransferaza asparaginianowa; **AVT** – *antiviral treatment*; **CKD** – *chronic kidney disease*; **D** – *donor*, dawca; **DAA-** *direct-acting antivirals***,** doustne leki o bezpośrednim działaniu przeciwwirusowym**; EASL -** *European Association for the Study of Liver Disease;* **ESRD** – *end-stage renal disease;* **HBV –** *hepatitis B virus*, wirus zapalenia wątroby typu B; **HCC –** *hepatocellular carcinoma***,** rak wątrobowo komórkowy**; HCV-** *hepatitis C virus*, wirus zapalenia wątroby typu C**; HD** – *hemodialysis***; KTx** – *kidney transplantation*, przeszczepienie nerki; **KTx HCV NAT D+/R- -** *kidney transplantation from HCV viremic donor to HCV aviremic recipient*, przeszczepienia nerki od dawcy z aktywną wiremią HCV biorcy HCV ujemnemu; **OCI** – *occult hepatitis C infection*, utajone wirusowe zapalenie wątroby typu C; **PBMC** – *peripheral blood mononuclear cells*, jednojądrzaste komórki krwi obwodowej; **PChN -** przewlekła choroba nerek**; R** – *recipient*, biorca; **RNA** – *rybonucleic acid*, kwas rybonukleinowy; **RT-PCR** – *real-time polymerase chain reaction*, łańcuchowa reakcja polimerazy w czasie rzeczywistym, **SNN –** schyłkowa niewydolność nerek**, SVR** – *sustained virologic response***,** trwała odpowiedź wirusologiczna**; WZW C –** wirusowe zapalenie wątroby typu C**; WZW B -** wirusowe zapalenie wątroby typu B

Wstęp

Szacuje się, że na świecie wirusem zapalenia wątroby typu C (HCV) jest zakażonych blisko 60 milionów ludzi, w tym około 140 tys. w Polsce. Pacjenci w przewlekłą chorobą nerek (PChN), szczególnie poddawani hemodializie oraz po przeszczepieniu nerki (KTx) stanowią szczególną subpopulację w tej grupie. Częstość występowania przewlekłego wirusowego zapalenia wątroby typu C (WZW C) znacząco przekracza tę obserwowaną w populacji ogólnej i szacowana jest na około 5-

10% dla pacjentów hemodializowanych oraz nawet 8-18% dla pacjentów po KTx. Wynika to z większej częstotliwości kontaktu wspomnianej grupy chorych z ochroną zdrowia, większą częstością hospitalizacji, narażeniem na procedury związane z przerwaniem ciągłości tkanek oraz w przypadku tych pierwszych nieprzestrzegania procedur mających na celu ograniczenie transmisji zakażenia w ramach stacji dializ. Potencjalne następstwa zakażenia są również znacząco bardziej wyrażone w populacji pacjentów z PChN. Oprócz następstw przewlekłego zakażenia HCV obserwowanych w populacji ogólnej pod postacią włóknienia i marskości wątroby, raka wątrobowokomórkowego (HCC), pacjenci z PChN są dodatkowo narażeni na gorszą jakość życia, krótsze przeżycie, szybszą progresję PChN, istotnie większe ryzyko zdarzeń sercowo-naczyniowych, a po transplantacji dodatkowo na szybszą utratę nerki przeszczepionej. Znajduje to odzwierciedlenie w aktualnych europejskich oraz amerykańskich wytycznych (European Association for the Study of Liver Disease (EASL) and American Association for the Study of Liver Disease (AASLD)), które jednoznacznie wskazują, że każdy pacjent z PChN zakażony wirusem HCV powinien zostać poddany leczeniu.

Przewlekle wirusowe zapalenie wątroby typu C stanowiło w przeszłości znaczące wyzwanie terapeutyczne szczególnie w grupie pacjentów z PChN. Dostępne w tym czasie terapie przeciwwirusowe oparte na interferonie były nie tylko mało skuteczne, ale pociągały też za sobą szereg działań niepożądanych. Stosowanie rybawiryny ograniczone było z kolei w znacznym stopniu przez niedokrwistość, która jest nierozerwalnie związana z PChN i była dodatkowo potęgowana działaniem leku. To wszystko skutkowało koniecznością redukcji jej dawki, bądź całkowitego odstawienia, a co za tym idzie bardzo często niepowodzeniem terapii. W 2014 roku do leczenia WZW C zostały wprowadzone doustne leki o bezpośrednim działaniu przeciwwirusowym (DAAs), których działanie polega na blokowaniu niestrukturalnych białek wirusa HCV odpowiedzialnych za jego replikację w zakażonych komórkach. Okazały się one nie tylko skuteczne, ale i dobrze tolerowane również w grupie pacjentów ze schyłkową niewydolnością nerek (SNN). Możliwe stało się także skrócenie czasu terapii. Doświadczenia oparte na terapii interferonowej oraz wielotygodniowe oczekiwanie na potwierdzenie osiągnięcia trwałej odpowiedzi wirusologicznej (SVR) skutkowały wątpliwościami dotyczącymi trwałości SVR osiągniętej w wyniku stosowania DAAs. Stąd dyskusja o ryzyku nawrotu zakażenia po zakończeniu terapii oraz odległym jej bezpieczenstwie.

Kilkuletnie już obserwacje udowadniają, że w przypadku terapii DAAs ryzyko reaktywacji zakażenia po osiągnięciu SVR jest znikome. Niewiele jest jednak badań dokumentujących trwałość efektu terapii w populacji pacjentów z PChN oraz po KTx, którzy przyjmują leki immunosupresyjne, a zatem są narażeni na większe domniemane ryzyko nawrotu. Jedna z publikacji należących do prezentowanego cyklu dokumentuje trwałość odpowiedzi wirusologicznej po 4 latach od zakończenia terapii i stanowi uzupełnienie wiedzy na temat skuteczności terapii DAAs w grupie pacjentów z PChN.

Tak jak wspomniano wcześniej, wprowadzeniu DAAs do terapii pacjentów z PChN towarzyszyły wątpliwości dotyczące potencjalnego bezpieczeństwa stosowanego schematu leczenia. Wątpliwości dotyczyły głównie zwiększonego ryzyka odrzucania nerki u pacjentów po KTx, potencjalnych interakcji z inhibitorami kalcyneuryny (CNI), czy nawrotu wirusowego zapalenia wątroby typu B (WZWB) . Wynikały one ze wstępnych doniesień o zwiększonym ryzyku powstania wyżej wspomnianych komplikacji po rozpoczęciu terapii DAAs. Kolejne badania, w tym przeprowadzona przez autorów analiza wskazały, że stosowanie DAAs w grupie pacjentów po Ktx jest bezpieczne i przy odpowiednim przygotowaniu pacjenta do terapii DAAs, uwzględniając potencjalne interakcje lekowe, w tym dostosowanie dawki CNI przed włączeniem leczenia, ryzyko wspomnianych wyżej komplikacji jest znikome. Nie zwalnia to jednak ze ścisłego monitorowania pacjentów w trakcie leczenia, a także po skutecznej eliminacji wirusa.

Doustne leki o bezpośrednim działaniu przeciwwirusowym mimo swojej imponującej skuteczności mogą łączyć się ze znaczącymi interakcjami lekowymi, w tym z CNI. Problem interakcji lekowych był najbardziej palący podczas stosowania DAAs pierwszej generacji, co rodziło konieczność ścisłego monitorowania stężenia leku oraz wielokrotnych i intensywnych modyfikacji dawki leków immunosupresyjnych. Duże wahania stężenia leku mogły narazić pacjentów na toksyczne działanie CNI, bądź odrzucanie narządu przeszczepionego. W ostatnim czasie możliwe stało się istotne ograniczenie tego ryzyko ze względu na wporwadzenie pangenotypowych DAAs. Należy jednak nadmienić, że dostęp do leków pangenotypowych nie jest powszechny, co powoduje, iż nie zawsze mogą być zastosowane. Prezentowany cykl publikacji podnosi również temat konieczności modyfikacji dawki CNI u pacjentów po przeszczepieniu nerki.

Nadrzędnym celem terapii przeciwwirusowej tuż obok osiągnięcia SVR jest ograniczenie odległych następstw przebytego zakażenia HCV, w tym śmiertelności i chorobowości. Dlatego też podczas kwalifikacji do leczenia przeciwwirusowego tak ważna jest ocena stopnia zaawansowania włóknienia wątroby. Im bardziej zaawansowane włóknienie tym większe ryzyko powikłań i rozwoju HCC. Nie ma zatem wątpliwości, że takich pacjentów powinno się kwalifikować do leczenia w pierwszej kolejności. Udowodniono, że w oparciu o ocenę włóknienia wątroby możliwe jest prognozowanie wątrobowych następstw WZW C, a tym samym dopasowanie zakresu i częstotliwości monitorowania pacjenta do spodziewanego ryzyka rozwoju powikłań. Włóknienie wątroby można ocenić przy użyciu różnorodnych metod. Najprościej można je podzielić na metody inwazyjne oraz nieinwazyjne, a pośród tych ostatnich można wyróżnić pośrednie i bezpośrednie. Najdokładniejszą metodą oceny włóknienia wątroby pozostaje badanie histopatologiczne bioptatu wątroby. Ograniczeniem wykorzystania tej metody jest jej inwazyjny charakter oraz możliwe powikłania, szczególnie u pacjentów z marskością wątroby. Ponadto łatwość nieinwazyjnych metod oceny włóknienia w korelacji z danymi klinicznymi w większości przypadków wyklucza potrzebę wykonywania biopsji. Z tego powodu coraz więcej uwagi poświęca się metodom nieinwazyjnym takim jak elastografia dynamiczna czy elastografia rezonansu magnetycznego. Ta ostatnia jest najdokładniejszą metodą spośród technik nieinwazyjnych. Ograniczenie wykorzystania tej metody wynika między innymi z wysokich kosztów oraz z wykorzystania pola elektromagnetycznego. Elastografia dynamiczna z kolei jest metodą zwalidowaną do oceny włóknienia wątroby w grupie pacjentów z WZW C i zalecaną szczególnie przy konieczności przeprowadzania powtarzanych pomiarów. Przeciwwskazania do wykorzystania elastografii dynamicznej są bardzo ograniczone, co pozwala na jej szerokie wykorzystanie oraz powtarzalność pomiarów w długofalowej obserwacji. Pośrednie wskaźniki włóknienia takie jak FIB-4 czy APRI są również wykorzystywane i rekomendowane w ocenie włóknienia u pacjentów z WZW C. Część badaczy wskazuje jednak, że po zakończonym leczeniu wymienione wskaźniki mogą odzwierciedlać stopień włóknienia wątroby ze znacznie mniejszą dokładnością. W badaniu autorów zostały wykorzystane zwalidowane i rekomendowane nieinwazyjne metody oceny włóknienia: elastografia dynamiczna oraz wskaźniki, APRI i FIB-4. W przeprowadzonej przez nas analizie udało się wykazać redukcję stopnia

włóknienia wątroby po skutecznej terapii DAAs, co jest zgodne z doniesieniami literaturowymi. Potwierdzona została również mniejsza korelacja wskaźników APRI i FIB-4 z elastografią dynamiczną przed i po leczeniu DAAs. Wynika to najpewniej z uwzględnienia we wzorach służących do wyliczenia wspomnianych wskaźników parametrów biochemicznych takich jak aminotransferaza asparaginianowa (AST) oraz aminotransferaza alaninowa (ALT), które gwałtownie spadają wraz z ograniczeniem aktywnego stanu zapalnego miąższu wątroby. Nie odzwierciedla to jednak faktycznej redukcji stopnia włóknienia wątroby.

Mając na uwadze, że w grupie pacjentów z PChN następstwa WZW C są znacznie poważniejsze w porównaniu do populacji ogólnej, a zaawansowanie włóknienia wątroby pozwala na prognozowanie ryzyka rozwoju powikłań czy HCC, celem tej pracy stało się określenie możliwego do osiągnięcia stopnia zahamowania, bądź regresji postępu włóknienia wątroby w wyniku zastosowania DAAs właśnie w tej kohorcie. Wstępne wyniki leczenia DAAs entuzjastycznie dokumentowały bardzo szybką redukcję włóknienia zaraz po zakończeniu leczenia. W trakcie dalszych obserwacji okazało się, że ocena włóknienia zaraz po osiągnięciu SVR w przeważającej części wynika z redukcji zapalenia a nie samego włóknienia, co mogło spowodować przeszacowanie redukcji stopnia włóknienia wątroby ocenianej metodami nieinwazyjnymi. Późniejsze prace udokumentowały, że spadek stopnia włóknienia może postępować w czasie nawet w kolejnych 5 latach po zakończeniu leczenia przeciwwirusowego w populacji ogólnej. Zdecydowaliśmy się zatem zweryfikować czy optymistyczne doniesienia o redukcji stopnia włóknienia wątroby znajdują odzwierciedlenie również w grupie pacjentów z PChN. Wedle najlepszej wiedzy autorów przeprowadzona przez nas analiza jest pierwszą oceniająca włóknienie wątroby w grupie pacjentów z PChN, która prezentuje wyniki przekraczające dwa lata obserwacji od zakończenia terapii.

W 2004 roku po raz pierwszy opisano jednostkę chorobową, jaką jest utajone zakażenie WZW typu C (OCI). Wyróżnia się dwa oddzielne typy utajonego zakażenia: pierwszy definiowany jest jako obecność materiału genetycznego wirusa w jednojądrzastych komórkach krwi obwodowej (PBMC) bądź tkance wątroby przy ujemnym wyniku przeciwciał anty-HCV oraz drugi, do którego odnosimy się w naszej pracy, związany z obecnością materiału genetycznego wirusa HCV w PBMC bądź tkance wątroby przy ujemnym oznaczeniu HCV RNA standardowymi metodami o zalecanym poziomi detekcji (<15 kopii/ml). Dane dotyczące znaczenia OCI oraz jego

implikacji klinicznych pozostają kontrowersyjne. Część badaczy wskazuje, że OCI skutkuje kryptogennym, postępującym uszkodzeniem wątroby, może być też źródłem transmisji zakażenia bądź nawrotu infekcji. Pojawiły się również sugestie, aby pacjenci z OCI pomimo osiągnięcia SVR byli poddawani ponownej terapii DAAs.

Częstość występowania OCI waha się od 0 do 83%. Tak duża rozbieżność wynika z różnorodności populacji pacjentów poddanych ocenie oraz braku standaryzacji metod detekcji HCV RNA stanowiących podstawę do rozpoznanie OCI. Populacje, które mogą być szczególnie narażone na możliwość wystąpienie OCI to pacjenci z obniżona odpornością, w tym dializowani oraz przyjmujący leczenie immunosupresyjne. Niewiele jest prac oceniających częstość występowanie OCI po skutecznej eradykacji wirusa HCV. Złotym standardem w diagnostyce OCI pozostaje biopsja wątroby, ale jej inwazyjny charakter oraz możliwość powikłań znacząco ogranicza jej zastosowania, szczególnie biorąc pod uwagę niepewny charakter ocenianych zmian. Dostępne badania wskazują, że eradykacja HCV RNA z PBMC i tkanki wątrobowej może trwać dłużej niż z surowicy oraz stwierdzana wiremia może mieć charakter falujący, dlatego wskazane są powtarzane oznaczenia, co zostało uwzględnione przy projektowaniu naszego badania; wykonano powtarzane oznaczenia HCV RNA w PBMC w odstępie dwóch do trzech miesięcy. Aby zróżnicować nawrót zakażenia od ukrytego zakażenia HCV w tym samym czasie oznaczeniu podlegało HCV RNA w surowicy.

Według doniesień literaturowych istnieją czynniki, które mogą wskazywać na zwiększone ryzyko wystąpienia OCI po osiągnięciu SVR i są one możliwe do zidentyfikowania przed włączeniem leczenia przeciwwirusowego: wysoka wiremia, aktywność ALT czy poprzednie terapie przeciwwirusowe w wywiadzie. W naszym badaniu nie było możliwe wskazanie czynników, które mogą zwiększać ryzyko OCI po osiągnięciu SVR ze względu na pojedynczy przypadek OCI w badanej populacji.

Należy podkreślić, że stwierdzenie materiału genetycznego wirusa HCV nie dowodzi jednoznacznie replikacji wirusa, a może wynikać z opóźnionej eliminacji wirusa z innych rezerwuarów ciała niż krew. Jednoznaczne potwierdzenie aktywnej replikacji wirusa jest możliwe poprzez potwierdzenie obecności ujemnej nici kwasu rybonukleinowego (RNA) wirusa HCV we krwi. W naszej pracy wykorzystana była metoda łańcuchowej reakcji polimerazy w czasie rzeczywistym (RT-PCR), która nie pozwala na różnicowanie między aktywną replikacją wirusa a przedłużoną eliminacją, co stanowi niewątpliwe ograniczenie przeprowadzonego badania. Aktualnie nie zaleca

się rutynowej diagnostyki w kierunku OCI, nie ma też ustalonego postępowania po ustaleniu rozpoznania. W świetle aktualnej wiedzy nie ma podstaw do weryfikacji aktualnych wytycznych dotyczących OCI.

W populacji pacjentów przyjmujących leki immunosupresyjne OCI może mieć większe znaczenie niż w populacji ogólnej ze względu na możliwość utrzymującej się przetrwałej wiremii oraz jej potencjalne następstwa. Przeprowadzona przez autorów analiza wskazuje, że po skutecznym leczeniu DAAs w grupie pacjentów z PChN w tym poddawanym leczeniu immunosupresyjnemu, ryzyko OCI jest niewielkie a jego implikacje kliniczne ograniczone. Niewątpliwym ograniczeniem badania jest brak tożsamych oznaczeń HCV RNA w tkance wątrobowej, gdyż w świetle dostępnej wiedzy największą czułość detekcji OCI zapewnia połączenie obydwu metod: oznaczania materiału genetycznego wirusa w PBMC i tkance wątrobowej.

Wprowadzenie DAAs przyczyniło się do znacznej redukcji liczby pacjentów z aktywnym WZW C. Mimo to w pierwszych latach stosowania DAAs leczenie pacjentów z PChN mogło stanowić wyzwanie ze względu na głównie nerkową drogę eliminacji sofosbuwiru. Pierwsze rekomendacje ograniczały możliwość jego stosowania u pacjentów z PChN i GFR < 30 ml/min/m^2pow.ciała. Aktualnie pacjenci hemodializowani nie stanowią już odrębnej grupy, a w świetle aktualnych, wspomnianych wcześniej zaleceń EASL oraz AASLD pacjenci ci mogą być leczeni zgodnie z wytycznymi dla populacji ogólnej. Jedynym ograniczeniem pozostaje w tej sytuacji dostęp do schematów pangenotypowych. Populacja pacjentów hemodializowanych powinna być jedną z najwdzięczniejszych populacji do osiągnięcia mikroeliminacji wirusa HCV pod kątem możliwości identyfikacji zakażenia, diagnostyki, kwalifikacji do leczenia przeciwwirusowego oraz samego włączenia terapii. Regularny kontakt z pacjentem umożliwia ścisłe monitorowanie leczenie oraz długofalową obserwację. Pomimo coraz większej ilości danych potwierdzających bezpieczeństwo stosowania DAAs w grupie pacjentów z PChN, w tym ze SNN, często nie znajduje to przełożenia na liczbę pacjentów, która jest poddawana leczeniu przeciwwirusowemu. Brak jest rzetelnych danych opisujących tę sytuację w Polsce oraz dotyczących praktyk stosowanych w stacjach dializ w odniesieniu do pacjentów z przewlekłym WZW C. Jedyne dane, które są corocznie aktualizowane i publikowane w raporcie podsumowującym stan dializoterapii w Polsce. Uwzględniają on jedynie liczbę pacjentów z dodatnim mianem przeciwciał anty-HCV oraz aktywną wiremią. Mając to na uwadze, zaprojektowaliśmy

badanie ankietowe, którego celem była odpowiedź na pytanie dotyczące sytuacji pacjentów dializowanych z towarzyszącym WZW C, a kwestionariusz ankiety posłużył nam jako narzędzie.

Przeprowadzone przez nas badanie jest pierwszym i jedynym znanym autorom dotyczącym aktualnie stosowanych praktyk w odniesieniu do pacjentów z przewlekłym WZW C w stacjach dializ w Polsce.

Preferowaną metodą leczenia SNN powinno być przeszczepienie nerki, pod warunkiem spełnienia odpowiednich kryteriów kwalifikacji. Organicznie zastosowania tej metody leczenia wynika z dysproporcji pomiędzy ciągle wzrastającą liczbą osób wymagających przeszczepienia nerki a niewystarczającą ilością dostępnych narządów. Wprowadzenie w latach 90 i szerokie stosowanie leków opioidowych doprowadziły do ich nadużycia, uzależnień powikłanych śmiercią, a opisane zjawisko wkrótce przybrało rozmiary epidemii. Efektem były liczne zgony, głównie wśród młodych osób bez przewlekłych chorób towarzyszących. Pojawiła się zatem nowa pula potencjalnych dawców i narządów do wykorzystania. Były one jednak i nadal są znacznie częściej odrzucane mimo często bardzo dobrej jakości narządu. Powodem jest częstsze w tej grupie współwystępowanie zakażenia HCV. Miało to związek z brakiem skutecznego leczeniem WZW C po przeszczepianiu nerki, a dostępne w przeszłości terapie interferonowe były przeciwwskazane po KTx. Sytuacja zmieniła się po wprowadzeniu DAAs. Dowiedziona skuteczność i bezpieczeństwo ich stosowania po przeszczepieniu narządów unaczynionych w tym nerki, pozwala na skuteczną eliminacje HCV również po transplantacji. Wobec niewystarczającej puli dawców przy wybitnej skuteczności DAAs możliwe staje się rozważenie przeszczepiania narządów od dawców z aktywną wiremią biorcom HCV ujemnym a przez to często skrócenie czasu oczekiwania na przeszczepienie i zmniejszenie śmiertelności w trakcie oczekiwania na narząd. Jest to bezpieczne i zasadne z medycznego punktu widzenia, ale wymaga regulacji prawnych, zapewnienia leczenia przeciwwirusowego oraz jasnych i spójnych wytycznych dotyczących między innymi selekcji potencjalnego biorcy czy czasu trwania terapii przeciwwirusowej. Dostępne dane pokazują, że pomimo szeregu ograniczeń, takie rozwiązanie powinno być wzięte pod uwagę szczególnie u chorych z długim przewidywanym czasem oczekiwania na transplantację np. wysokoimmunizowanych. Jest to stosunkowo nowe podejście do ograniczonej liczby narządów i powszechnie jeszcze nieakceptowane. Podjęliśmy zatem próbę

podsumowania dotychczasowych wyników badań przeszczepienia nerki od dawcy z aktywną wiremią HCV biorcy HCV ujemnemu (KTx HCV NAT D+/R-) z jego zaletami i ograniczeniami. W czasie, kiedy powstawała praca poglądowa podsumowująca efekty przeszczepienia KTx HCV NAT D+/R-, wprowadzenie takie standardu postępowania wydawało się przedwczesne. W chwili obecnej przy ciągle rosnącej ilości publikacji potwierdzającej korzystne krótko- jak i długoterminowe efekty tej praktyki w opinii autorów KTx HCV NAT D+/R- mogłoby zostać wprowadzone jako standard postępowania, pod warunkiem szczegółowego przeprowadzenia procesu świadomej zgody oraz niezwłocznego zapewnienia leczenia przeciwwirusowego tuż po potwierdzeniu wiremii lub wyprzedzająco przed pojawieniem się replikacji w ramach profilaktyki przeciwwirusowej.

Z dostępnych badań wynika, że pacjenci oczekujący na przeszczepienie nerki w pierwszej kolejności polegają na opinii swojego nefrologa w kwestiach związanych z przeszczepieniem nerki, dlatego też w ankiecie zadaliśmy pytanie dotyczące opinii nefrologów dotyczącej wykorzystania narządów od dawców z aktywną wiremią HCV.

Prezentowany cykl publikacji tworzy spójną całość oraz dowodzi złożoności i wielowątkowości zagadnienia jakim jest przewlekłe WZW C w grupie pacjentów z PChN. W szerokim ujęciu prezentuje kwestie związane ze skutecznością i bezpieczeństwem stosowania DAAs w grupie pacjentów z PChN wraz z potencjalnymi możliwościami, które dzięki temu się otwierają.

W pierwszyej publikacji oceniamy skuteczność i bezpieczeństwo leczenia WZW C w grupie pacjentów dializowanych. W naszej pracy zarówno na skuteczność jak i bezpieczeństwo terapii patrzymy bardzo szeroko. Oceniane jest zarówno SVR, OCI po zakończonym leczeniu przeciwwirusowym, ale również potencjał odwracalności włóknienia wątroby. Ocena bezpieczeństwa również opiera się na podobnych założeniach. Wnikliwie analizujemy nie tylko działania niepożądane czy konieczności dostosowania dawki CNI w trakcie leczenia, ale także czynność nerki przeszczepionej, możliwe odrzucanie narządu przeszczepionego, czy ryzyko rozwoju HCC.

W kolejnej pracy weryfikujemy czy pacjenci z PChN zakażeni HCV są poddawani leczeniu i analizujemy prawidłowość postępowania po zakończonym leczeniu. Cykl publikacji zamyka przegląd literatury opisującej wykorzystanie narządów od dawców zakażonych wirusem HCV w leczeniu biorców HCV ujemnych, uwzględniając ograniczenia oraz zalety tego podejścia.

Założenia i cel pracy

1. Ocena skuteczności leczenia przewlekłego wirusowego zapalenia wątroby typu C u pacjentów z przewlekłą chorobą nerek w schemacie bezinterferonowym
2. Ocena bezpieczeństwa leczenia przewlekłego wirusowego zapalenia wątroby typu C u pacjentów z przewlekłą chorobą nerek w schemacie bezinterferonowym.
3. Analiza interakcji pomiędzy grupą nowych doustnych leków o bezpośrednim działaniu przeciwwirusowym stosowanych w leczeniu przewlekłego wirusowego zapalenia typu C, a inhibitorami kalcyneuryny, podstawową grupą leków stosowanych u chorych po transplantacji nerek.
4. Analiza wpływu leków o bezpośrednim działaniu przeciwwirusowym w leczeniu przewlekłego wirusowego zapalenia wątroby typu C na czynność nerki przeszczepionej oraz włóknienie wątroby.
5. Analiza praktyk związanych z diagnostyką, leczeniem i monitorowaniem pacjentów hemodializowanych z przewlekłym zapaleniem wątroby typu C w stacjach dializ w Polsce.

Uwagi: Wstępne założenia pracy doktorskiej zawierały również porównanie skuteczności różnych schematów leczenia przewlekłego wirusowego zapalenia wątroby typu C u pacjentów z identycznym genotypem wirusa oraz ustalenie optymalnego schematu leczenia przewlekłego wirusowego zapalenia wątroby typu C u chorych po zabiegu przeszczepienia alogennej nerki. Dynamiczny rozwój w dziedzinie możliwości leczenia WZW C oraz wprowadzenie leków pangenotypowych spowodował, że powyższe cele straciły na znaczeniu w świetle aktualnie wiedzy oraz dostępnych możliwości leczenia i nie stanowiły wartości dodanej dla prezentowanych wyników analizy ani przedstawionego cyklu publikacji. Z pełną świadomości odstąpiono zatem od szczegółowej analizy w tym zakresie.

Streszczenie w języku polskim

Publikacja 1: Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?

Praca Poglądowa

Przeszczepienie nerki jest optymalną metodą leczenia schyłkowej niewydolności nerek. Nie może być ono jednak zawsze wdrożone ze względu na ograniczoną liczbę narządów dostępnych do przeszczepienia. Wprowadzenie DAAs do terapii WZW C umożliwiło zwiększenie liczby transplantacji poprzez wykorzystanie narządów od dawców z aktywną wiremią. Najnowsze doniesienia dowodzą zadowalających wstępnych wyników przeszczepień z wykorzystaniem narządów od dawców replikujących, w tym nerek. Pomimo coraz większej liczby dostępnych publikacji na ten temat nadal narządy od dawców HCV dodatnich wielokrotnie nie są akceptowane do dawstwa, a wiodącą przyczyną jest obecności przeciwciał anty-HCV. Takie podejście wynika najpewniej z ograniczonej wiedzy na temat ryzyka zakażenia, powikłań z tym związanych oraz możliwości profilaktyki i leczenia po przeszczepieniu narządu z aktywną wiremia HCV.

Celem pracy było podsumowanie możliwości i bezpieczeństwa jakie stwarza wykorzystanie narządów od dawców z aktywną wiremią HCV w leczeniu biorców HCV ujemnych oraz ograniczeń z nim związanych w świetle aktualnej wiedzy medycznej. W tym celu dokonany został przegląd dostępnej literatury.

W świetle aktualnej wiedzy medycznej KTx HCV NAT+ D+/R- może stanowić potencjalne rozwiązanie dysproporcji między potrzebami a niewystarczającą liczbą organów dostępnych do przeszczepienia. Należy mieć jednak świadomość ryzyka rozwoju powikłań. Niezbędne jest zapewnienie DAAs bez zbędnej zwłoki oraz odpowiednia kwalifikacja biorcy. Konieczne jest również ujednolicenie standardów postępowania po takiej procedurze.

Narządy od dawców z aktywną wiremią HCV powinny zostać w pierwszej kolejności wykorzystane w celu leczenia biorców z WZW C. Takie podejście łączy się z niższymi kosztami leczenia , mniejszym ryzykiem możliwych powikłań oraz jest zasadne z etycznego punktu widzenia. Narządy, w tym nerki od dawców HCV

dodatnich powinny być proponowane biorcom HCV ujemnym dopiero w drugiej kolejności.

Podsumowując, aktualnie wprowadzenie KTx HCV NAT+ D+/R- jako standardu postępowania wydaje się przedwczesne. Potrzebne są dalsze badania, aby ocenić długofalowe konsekwencje tej praktyki.

Publikacja 2: Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey

Przewlekłe zakażenie WZW typu C znamiennie częściej występuje w populacji pacjentów dializowanych. Wszyscy pacjenci z przewlekłym WZW C powinni być kierowani do leczenia przeciwwirusowego, co podkreśla również cel wyznaczony przez Światową Organizację Zdrowia: eliminacji wirusa HCV do 2030 roku. Mimo to wielu pacjentów hemodializowanych nadal nie jest poddawanych leczeniu.

Należy podkreślić, że nawet po skutecznej eliminacji wirusa HCV nadal konieczne jest odpowiednie monitorowanie włóknienia wątroby oraz pod kątem rozwoju HCC, aby zapewnić redukcję śmiertelności z przyczyn wątrobowych czy onkologicznych. Jest to szczególnie ważne u pacjentów z wyjściowym zaawansowanym włóknieniem wątroby oraz marskością. Przeprowadzone badanie miało na celu określenie praktyk związanych z leczeniem i monitorowaniem pacjentów hemodializowanych z WZW C oraz przeszkód, które mogą utrudniać eliminację wirusa HCV w tej populacji.

W celu przeprowadzenia badania stworzyliśmy kwestionariusz ankiety, który został przesłany drogą elektroniczną do wszystkich stacji dializ w Polsce. Badanie było prowadzone anonimowo pomiędzy styczniem a grudniem 2022 roku. Każda stacja dializ była reprezentowana przez jednego przedstawiciela. Kwestionariusz był przesyłany do kierownika jednostki, który był proszony o jego uzupełnienia.

Uzyskano odpowiedzi ze 112 stacji dializ, co stanowi 43.1% wszystkich stacji dializ w Polsce, które mają pod swoją opieką łącznie 43.4% pacjentów hemodializowanych. Prawie wszyscy respondenci, byli kierownikami stacji dializ i posiadali specjalizację z nefrologii. Przeprowadzone badanie pokazało, że większość stacji dializ (91.6%)

rutynowo bierze pod uwagę możliwość leczenia przeciwwirusowego u swoich pacjentów. Wykazano jednak wiele czynników ograniczających, które skutkują tym, że pacjenci ostatecznie nie otrzymują leczenia. Najczęściej wymieniana była niechęć pacjentów do poddania się leczeniu przeciwwirusowemu (40.6%) oraz przeciwwskazania do stosowania DAAs (18.8%). Interakcje lekowe zostały wskazane tylko przez 3% respondentów. Uzyskane wyniki są zaskakujące, ponieważ w świetle aktualnej wiedzy i dostępności leków pangenotypowych, przeciwwskazania do stosowania DAAs są bardzo ograniczone. Z kolei interakcje lekowe, które wydają się wiodącym problemem w przypadku wielochorobowości pacjentów hemodializowanych zostały wskazane w zdumiewająco niskim odsetku przypadków. Dostępne terapie przeciwwirusowe są skuteczne i dobrze tolerowane, zdumiewający jest zatem wysoki odsetek niechętnych pacjentów do poddania się leczeniu przeciwwirusowemu. Ze względu na konstrukcję badania nie było możliwe zweryfikowanie czynników decydujących o niechęci pacjentów.

Przeprowadzona analiza wykazała, że większość stacji dializ nie ocenia rutynowo włóknienia wątroby u pacjentów hemodializowanych z WZW C (60.4%), ani nie monitoruje ich w pod kątem rozwoju HCC (53.5%). Prawie połowa ankietowanych stacji dializ deklarowała prowadzenie leczenia nerkozastępczego pacjentów po osiągnięciu SVR przy użyciu maszyn dedykowanych pacjentom HCV ujemnym (46.7%), niewiele mniej (40.6%) stacji wskazało jednak, że po eliminacji wirusa stanowisko leczenie nerkozastępczego nie jest weryfikowane i jest w dalszym ciągu prowadzone na miejscu dla chorych zakażonych wirusem HCV.

Przedstawione badanie pokazuje, że praktyki dotyczące leczenia i monitorowania pacjentów z WZW C znacząco się różnią w skali kraju. W opozycji do optymistycznych danych wskazujących na dużą liczbę pacjentów hemodializowanych rozważanych jako potencjalni kandydaci do leczenia przeciwwirusowego, pozostaje duża ilość przeszkód pojawiających się przed pacjentami na drodze do otrzymania przez pacjenta DAAs, a tym samym skutecznej eliminacji wirusa. Całość obrazu wskazuje na niewystarczającą wiedzę nefrologów dotyczącą postępu, jaki dokonał się w zakresie możliwości leczenia oraz opieki nad pacjentem z WZW C. Możemy przypuszczać, że znalazło to przełożenie na niechęć pacjentów do poddania się leczeniu. Konieczne jest również zoptymalizowanie oraz ukierunkowanie opieki nad pacjentami z WZW C w stacjach dializ w Polsce.

Publikacja 3: Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study.

Populacja pacjentów z PChN jest szczególnie narażona na niekorzystne następstwa zakażenia WZW C. Doustne leki o bezpośrednim działaniu przeciwwirusowym są z powodzeniem stosowane w celu eliminacji wirusa w tej populacji, ale długofalowe efekty nie są do końca poznane.

Celem przeprowadzonego badania była ocena efektów leczenia przewlekłego WZW C w schemacie bezinterferonowym w grupie pacjentów z PChN. Oceniana było zarówno skuteczność jak i bezpieczeństwo zastosowanego leczenia.

Przeprowadzono jednoośrodkowe retrospektywne badanie kohortowe, do którego włączono pięćdziesięciu dziewięciu pacjentów z przewlekłym WZW C oraz PChN (dializowanych oraz po przeszczepieniu nerki), którzy w latach 2016-2018 zostali poddani leczeniu przeciwwirusowemu w schemacie bezinterferonowym. Ocenę skuteczności i bezpieczeństwa przeprowadzono między innymi w oparciu o SVR, występowanie OCI oraz dynamikę włóknienie wątroby (przed oraz 4 lata po zakończeniu terapii przeciwwirusowej).

Trwałą odpowiedź wirusologiczną osiągnęło 96% pacjentów. Utajone zakażenie HCV potwierdzono u jednego pacjenta po trzecim KTx z wywiadem licznych przetoczeń preparatów krwiopochodnych w nieodległym czasie przed wykonanymi oznaczeniami w kierunku OCI. Materiał genetyczny wirusa HCV w PBMC stwierdzono w obydwu punktach czasowych, nie stwierdzając jednocześnie żadnych cech postępującego uszkodzenia wątroby. W okresie czteroletniej obserwacji w badanej populacji odnotowano niemalże 20% redukcję włóknienia wątroby w porównaniu do wartości wyjściowych. Najczęściej obserwowanymi działaniami niepożądanymi była niedokrwistość, osłabienie oraz zakażenie układu moczowego. Niedokrwistość po włączeniu leczenia DAAs była raportowana jedynie u pacjentów leczonych rybawiryną i w każdym przypadku zmuszała do redukcji dawki, bądź jej odstawienia. Dominującą częścią badanej populacji byli pacjenci po przeszczepieniu nerki. Zakażenia układu moczowego są najczęstszym powikłaniem obserwowanym u pacjentów po KTx. Żadne z nich nie było związane z prowadzonym

leczeniem przeciwwirusowym i nie skutkowało przerwaniem terapii, a czynność nerki przeszczepionej pozostała stabilna do 2 lat po zakończeniu terapii.

Podsumowując, DAAs charakteryzują się dużą skutecznością oraz korzystnym profilem bezpieczeństwa w populacji pacjentów z PChN w przedłużonej obserwacji.

Streszczenie w języku angielskim

Publication 1: Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?

Narrative Review

Kidney transplantation is the treatment of choice in end-stage renal disease. The main issue which does not allow to utilize it fully is the number of organs available for transplant. Introduction of highly effective oral direct-acting antivirals (DAAs) to the treatment of chronic hepatitis C virus infection (HCV) enabled transplantation of HCV viremic organs to naïve recipients. Despite an increasing number of reports on the satisfying effects of using HCV viremic organs, including kidneys, they are more often rejected than those from HCV negative donors. The main reason is the presence of HCV viremia and not the quality of the organ.

This study focuses on the possibilities created by the usage of HCV-viremic donor organs based on current medical knowledge and on additional aspects that limit the usage of such donor organs. A critical literature review was performed along with available outcomes of the KTx HCV NAT D+/R-.

In light of the current knowledge, the transplantation of HCV NAT + kidneys to naïve recipients may constitute a solution to organ shortage. However, such practice entails a risk of complications, especially when combined with the difficulty in providing DAA therapy in the direct posttransplant period and the need for careful recipient selection.

It is rational to prioritize the utilization of HCV NAT + organs in recipients already infected with HCV. This entails lower costs, limits the risk of possible complications, and seems more reasonable from an ethical standpoint. Such organs should be offered to HCV-negative recipients only as a secondary choice. However, this is not always possible in everyday practice.

Currently, it seems premature to utilize HCV NAT D+/R- kidney transplantation as a standard of care. Further studies are required to draw solid conclusions regarding the long-term consequences of adopting such a treatment approach.

Publication 2: Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey

Chronic hepatitis C (CHC) is prevalent in the hemodialysis-dependent population. Currently, all patients with CHC should be considered for treatment; however, many hemodialysis-dependent patients are still left untreated.

Following HCV cure, accurate liver fibrosis and HCC surveillance is mandatory to reduce liver-related mortality and risk of oncological complications. It is of upmost importance in patients with advances liver fibrosis or cirrhosis at baseline. The aim of this study was to investigate the HCV management practices across dialysis centers in Poland and identify potential barriers that prevent us from reaching the goal of HCV elimination by 2030. We strongly believe that identifying obstacles could be the first step toward HCV elimination in the end-stage renal disease (ESRD) population in Poland.

All adult hemodialysis (HD) centers in Poland, which were active in 2022 (n = 260), were approached for the survey via email, and only one representative (medical doctor) of each unit was to complete the survey. Each HD center was represented only once. The survey was performed anonymously.

Representatives of 112 dialysis centers responded, representing 43.1% of all dialysis centers in Poland and 43.4% of hemodialysis-dependent patients' volume. Most respondents were Heads of hemodialysis centers and board-certified nephrologists. The study demonstrated that in the vast majority of HD centers (91.6%), subjects are

considered for antiviral treatment (AVT); however, many obstacles preventing patients from being prescribed AVT were identified; patients' reluctance to undergo AVT was most reported (60%). Surprisingly many responders pointed to contraindications to AVT (18.8%) as a reason for not treating the patient compared to drug-drug interactions (3%). With the current AVT armamentarium, contraindications are very limited and mostly related to interactions with concomitant medication. We may presume that those results may similarly stem from little expertise on the current CHC treatment landscape. Owing to the anonymous nature of the survey, we were not able to verify with responders which contraindication they were referring to specifically.

The majority of dialysis units neither evaluate patients with CHC for liver fibrosis (60.4%) nor screen them for hepatocellular carcinoma (53.5%). Virtually half of the responders declared that they managed patients with CHC following SVR on machines that were dedicated for patients HCV naïve (46.7%), while similar percentage of HD centers (40.7%) placed them on machines dedicated for patients with hepatitis.

In conclusion, the presented study demonstrates that HCV management practices across Polish dialysis centers vary substantially. An impressive percentage of HD centers that consider patients for AVT may seem to be overly optimistic considering multiple obstacles hindering ESRD patients from received AVT and may not yield desirable effects in the form of HCV elimination. There is a need to improve nephrologist awareness of HCV care standards to allow for knowledgeable patient management in this area. We may speculate that the subject's averseness towards DAAs, at least to some extent, stems from a lack of expertise among dialysis physicians There is a need to optimize and streamline the HCV management infrastructure in the hemodialysis population in Poland.

Publication 3: Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study.

The chronic kidney disease (CKD) population, including kidney transplant recipients and subjects on renal replacement therapy, is particularly vulnerable to unfavorable outcomes from CHC. Currently, there are oral direct-acting antiviral agents available to eradicate the virus with favorable short-term outcomes; however, their long-term

effects are lacking. The aim of the study is to assess the long-term efficacy and safety of DAA therapy in the CKD population.

This was an observational, cohort single-center study. Fifty-nine CHC subjects with CKD, treated with DAAs between 2016 and 2018, were enrolled in the study. Safety and efficacy profiles were assessed, including SVR, OCI incidence, and liver fibrosis dynamics following SVR.

SVR was achieved in 96% of cases (n = 57). OCI was diagnosed only in one subject following SVR The patient had this third kidney transplant and had multiple blood-derived products administered prior to OCI samples collection. Occult HCV was confirmed in both PBMC samples, but no evidence of liver injury was present. Significant liver stiffness regression was observed 4 years after SVR compared to baseline values. The most common adverse events were anemia, weakness, and urinary tract infection. Anemia was observed only in RBV-treated subjects and mandated dose reduction or discontinuation in all subjects receiving RBV. The vast majority of our study population comprised KTRs, and it has been previously documented that infections are the most prevalent complication following KTx, with UTI being the most frequent. No UTIs were AVT-related and kidney function remained stable for the duration of AVT and until 2 years after SVR.

In conclusion, DAAs provide a safe and effective cure for CHC in both CKD patients and KTRs with a favorable safety profile in the long-term follow-up.

Podsumowanie i wnioski

Na podstawie zarysowanych założeń przeprowadzona przez autorów analiza potwierdza, że leczenie WZW C z wykorzystaniem terapii bezinterferonowej w populacji pacjentów z PChN ze szczególnym uwzględnieniem chorych dializowanych i po przeszczepieniu nerki pozwala na skuteczną oraz trwałą eliminację wirusa HCV. DAAs wykazują korzystny profil bezpieczeństwa, a notowane działania niepożądane mają niewielkie nasilenie, co za tym idzie ryzyko przerwania leczenia jest znikome. Szczególnie istotnym wnioskiem jest to, że w badanej grupie stosowanie

DAAs nie zwiększa ryzyka odrzucenia przeszczepu, niepowodzenia terapii przeciwwirusowej oraz wystąpienie HCC. W długoterminowej obserwacji pacjenci po osiągnięciu SVR uzyskują zahamowanie oraz cześciową redukcję włóknienia wątroby, a tym samym ograniczenie ryzyko odległych niekorzystnych następstw WZW C.

Przeprowadzone badanie ankietowe wykazało, że korzystne odległe obserwacje po zakończonym leczeniu DAAs, nie przekładają się na poprawę opieki nad pacjentami dializowanymi w stacjach dializ w Polsce. Mimo deklaracji rozważenia pacjentów z WZW C, jako potencjalnych kandydatów do leczenia wiele wątpliwości pozostawia rzeczywista opieka nad chorymi.

Niezadowalająca pozostaje opieka nad pacjentami, którzy leczeniu nie zostali poddani jak i tymi, którzy skutecznie je zakończyli. Takie podejście nie pozwala na wykorzystanie potencjału DAAs na możliwy wzrost przeżywalności i redukcję chorobowość w grupie pacjentów dializowanych. Konieczne są jasne wytyczne oraz rekomendacje wyznaczające standardy opieki nad pacjentem dializowanym z aktywną wiremią HCV, po skutecznym leczeniu przeciwwirusowym oraz rozważenie wprowadzenia okresowej oceny włóknienia wątroby u wszystkich pacjentów z WZW C w ramach stacji dializ. Niezbędne wydaje się również szkolenie lekarzy stacji dializ w zakresie możliwości terapeutycznych oraz obserwacji długoterminowej w tej grupie chorych ze szczególnym uwzględnieniem oceny włóknienia wątroby.

Przedstawione w przeglądzie literatury zachęcające wstępne wyniki przeszczepiania nerek od dawców z aktywną wiremią HCV biorcom HCV ujemnym wskazują potencjalne rozwiązanie na zmniejszenie śmiertelności pacjentów oczekujących na liście na zabieg przeszczepienia nerki, która szacowana jest nawet na 25%. Wykorzystanie nerek z aktywną wiremią stało się możliwe, dzięki skuteczności i korzystnemu profilowi bezpieczeństwa DAAs, czego dowodzi przedstawiona praca oceniająca odległe skutki leczenia WZW C z wykorzystaniem terapii bezinterferonowych.

Przeprowadzona analiza pozwoliła uzupełnić luki wiedzy szczególnie związane z monitorowaniem pacjentów z towarzyszącym WZW C w stacjach dializ w Polsce, oraz uwidocznić jak niedocenionym i niewykorzystanym narzędziem w walce o poprawę jakości życia pacjentów hemodializowanych są DAAs.

RENAL FAILURE
2022, VOL. 44, NO. 1, 434–449
https://doi.org/10.1080/0886022X.2022.2047069

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STATE-OF-THE-ART REVIEW

Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?

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ABSTRACT

Kidney transplantation is the treatment of choice in end-stage renal disease. The main issue which does not allow to utilize it fully is the number of organs available for transplant. Introduction of highly effective oral direct-acting antivirals (DAAs) to the treatment of chronic hepatitis C virus infection (HCV) enabled transplantation of HCV viremic organs to naive recipients. Despite an increasing number of reports on the satisfying effects of using HCV viremic organs, including kidneys, they are more often rejected than those from HCV negative donors. The main reason is the presence of HCV viremia and not the quality of the organ. The current state of knowledge points to the fact that a kidney transplant from an HCV nucleic acid testing positive (NAT+) donor to naive recipients is an effective and safe solution to the problem of the insufficient number of organs available for transplantation. It does not, however, allow to draw conclusions as to the long-term consequence of such an approach. This review analyzes the possibilities and limitations of the usage of HCV NAT + donor organs.

Abbreviations: DAA: direct-acting antivirals; HCV: hepatitis C virus; NAT: nucleic acid testing; OPTN: Organ Procurement and Transplantation Network; KDIGO: Kidney Disease: Improving Global Outcomes; Ab: antigen; eGFR: estimated glomerular filtration rate; D: donor; R: recipient; CMV: cytomegalovirus; HBV: hepatitis B virus; UNOS: United Network for Organ Sharing; PHS: Public Health Service; EBR/GZR: elbasvir/grazoprevir; SVR: sustained virologic response; RAS: resistance-associated substitutions; SOF: soforbuvir; GLE/PIB: glecaprevir/pibrentasvir; ACR: acute cellular rejection; AR: acute rejection; DSA: donor-specific antibodies; KTR: kidney transplant recipients; AASLD: American Association for the Study of Liver Disease; IDSA: Infectious Diseases Society of America; PPI: proton pump inhibitors; CKD: chronic kidney disease; GN: glomerulonephritis; KAS: The Kidney Allocation system

ARTICLE HISTORY
Received 22 November 2021
Revised 3 February 2022
Accepted 21 February 2022

KEYWORDS
Renal transplantation; hepatitis C; antiviral drugs; organ donors

Introduction

Kidney transplantation is the treatment of choice for patients with end-stage renal disease. It not only reduces mortality in this group of patients but also improves their quality of life. However, the demand for transplant organs far exceeds their availability. According to data published by the Organ Procurement and Transplantation Network (OPTN), more than 90,000 people are awaiting a kidney transplant [1]. Importantly, dialysis-dependent patients have a higher mortality rate compared to general population which is mostly attributable to cardiovascular disease [2]. As a result, many of kidney transplant candidates will not survive until they obtain a transplant [3]. This is the result of a long waiting time for an organ, which in the US can extend to 3–5 years [4].

Many steps are being taken to increase the organ donor pool including living donors and donors after cardiac death. Despite this, demand for organs still exceeds the supply. Another step taken in order to resolve the organ shortage issue is also the use of organs from donors infected with the hepatitis C virus (HCV). The advent of new, highly effective interferon-free therapies with an efficacy exceeding 95% allowed to utilize HCV-viremic organs especially in the setting of significant increase in mortality resulting from drug overuse, opioids in particular, in the US [5]. These donors have a higher prevalence of HCV viremia compared to standard risk criteria donors. Donors infected with HCV are usually younger than HCV-negative donors, and this can result in fewer comorbidities and improved quality of the organ, as manifested by the

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Kidney Donor Profile Index (KDPI) [6–9]. The use of organs from HCV donors with active viremia could also increase the donor pool of kidneys available for transplantation by as many as 500 organs per year [10].

In the past, HCV infection in a donor was considered a contraindication for kidney transplantation owing to the risk of long-term immunosuppression in the recipient. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, since the 1990s, kidneys from HCV antibody-positive (Ab+) donors have been used as transplants under the condition that the recipient is also HCV Ab+. However, owing to the difficulty in differentiating donors with and without active viremia and lack of highly effective treatments, the use of such organs was limited [11]. The current guidelines of the American Society of Transplantation do not forbid the transplantation of infected organs to recipients not infected with HCV, but they indicate the necessity for further research on the consequence of such a practice [12].

This study focuses not only on the possibilities presented by the usage of HCV-viremic donor organs based on current medical knowledge, but also on additional aspects that limit the usage of such donor organs.

Underutilization

In the past, HCV-positive organs were discarded nearly three times more often than HCV-negative ones were [13]. Between 2005 and 2014, although 6456 kidneys from HCV-seropositive donors were available for transplantation, only 37% of them were actually transplanted [10]. However, only approximately 16% of them would have been HCV viremic.

Data from the UK indicate that in as many as 76% of cases, the only cause for discarding the organ was the serological status of the donor, and only 8.9% were discarded because of the unsatisfactory condition of the organ itself [14]. This could have resulted from the fear of transmitting HCV infection as well as the findings of studies showing worse results for transplants from HCV-positive donors to HCV-negative recipients. However, such data are from a period when the treatment of HCV was purely interferon-based. In their retrospective data analysis of the OPTN registries, La Hoz et al. compared the results of kidney transplantation from HCV NAT + and HCV Ab+/NAT− donors in relation to those from HCV-negative donors [15]. They reported better kidney function as manifested by estimated glomerular filtration rate (eGFR) within 6 months after transplantation, a comparable 12-month graft survival rate, and lower frequency of acute rejection (AR) events.

The tendency to discard HCV-positive organs is visibly changing. Within the first 3 months of 2019, 200 kidneys were transplanted into HCV-negative recipients from HCV NAT + donors [16]. However, the odds of discarding HCV-viremic kidneys was 48% higher than the odds for discarding HCV-negative kidneys [17]. The latest survey on US transplant programs revealed that 58% of transplant centers offered transplantation from an HCV-viremic donor to an HCV-negative recipient (HCV D+/R-) [18]. The authors reported difficulties in insurance coverage as the primary factor that hindered the utilization of HCV-viremic kidneys in naïve recipients. Anderson et al., in turn, reported that the most discouraging factor was the risk of virus transmission (59%) and, most probably, the fear of possible complications; however, in 14% of cases, the main factor was the risk of being sued and in 3% of cases, it was a previous negative experience [19].

Until recently, HCV-viremic organs were offered to HCV-negative recipients only within clinical trials, for a carefully selected group of patients with guaranteed access to direct antiviral agents (DAAs). Significant shortening of the time spent on a waiting list and encouraging outcomes of HCV NAT D+/R- transplantations translated to the utilization of this practice as a standard of care by 14% of transplant centers according to the latest national survey [18].

The approach to HCV NAT D+/R− transplantation varies across European countries and depends on the national organ transplant program. Recommendations regarding HCV NAT testing are not unified and vary on other continents. In the authors' country, HCV NAT D+/R− transplantation are against the national law; hence, HCV-seropositive organs are offered solely to HCV-positive recipients and a separate consent is required. Presence of viremia is verified after transplantation.

The underutilization of HCV NAT + organs can seem surprising when compared to the utilization of organs with the risk of transmission of viruses such as hepatitis B virus (HBV) or cytomegalovirus (CMV), which, despite the introduction of appropriate treatment, can result in *de novo* hepatitis and a higher risk of death after transplantation, an increased risk of rejection, or opportunistic infections by HBV and CMV [20–22] Despite this, both CMV D+/R− and anti-HBc + D+/R− organs are accepted for transplantation because of the larger survival benefits for the patient than the risks resulting from the transmission of the virus. This underscores a need for raising awareness of the HCV- viremic organs utilization and efficacy of DAAs.

HCV testing and risk of transmission

The attitude toward an HCV-positive donor has completely changed with the introduction of obligatory testing for HCV RNA (NAT) as part of HCV infection diagnostics, in addition to the serological tests mandated by the United Network for Organ Sharing (UNOS) for potential organ donors in US [12]. This allowed the identification of donors with active viremia (HCV Ab+/NAT + or HCV Ab-/NAT+) and those without it (HCV NAT-). Such differentiation of donors is key because not every HCV-positive donor poses a risk of virus transmission through transplantation.

HCV Ab+/NAT- donors are those in whom the virus has been eradicated spontaneously or through antiviral treatment. Spontaneous eradication of the virus is possible in up to 45% of cases, but non-immunocompetent patients have a smaller chance for spontaneous eradication [23,24]. Kidney transplantation from an HCV donor (Ab+/NAT-) to an HCV-negative recipient can result in seroconversion, but the risk of viremia is minimal. Although the risk of viral transmission is low, screening for HCV viremia is advisable in an early post-transplant period.

In contrast, HCV NAT + donors, regardless of their serological status, are patients with active viremia and account for 4.2% of donors in the US [25]. HCV viremia in the donor is associated with a high risk of virus transmission. Viremia always develops in recipients after HCV D+/R- NAT liver transplants, and almost always in the case of heart, lung, or kidney transplants [26–31].

The introduction of routine HCV NAT testing helped reduce the diagnostic window, in which HCV infection is present but cannot yet be identified, from to 2–6 months for serological assays to 5–7days for NAT, thereby limiting the risk of unintentional virus transmission from an organ donor. Nonetheless, the nonintentional transmission of the virus from the donor to the recipient persists, especially in the case of donors meeting the US Public Health Service (PHS) criteria. Despite a negative serological result, the residual risk ranges from 0.26 to 300.6 for every 10000 donors and ranges from 0.027 to 32.4 for every 10000 donors when NAT is utilized [32]. Suryaprasad et al. described three cases of nonintentional HCV transmission despite a negative NAT result for the donor [33]. In this case, majority of the recipients were infected with HCV through the transplanted organ. Interestingly, at least three of the 12 recipients did not develop an HCV infection. This could point to the existence of factors other than the transplanted organ being responsible for the infection, but none have yet been identified.

The current guidelines of the US PHS have further recommendations on how to minimize the risk related to the utilization of organs from PHS criteria donors. The recommendation is to test all donors for human immunodeficiency virus, HCV, and HBV infections using NAT [34].

Kidney transplantation from HCV-viremic donors to HCV-aviremic recipients

The efficacy of HCV NAT D+/R- kidney transplantation has been reported in several clinical trials [35–40]. The first prospective studies assessing the efficacy and safety of utilizing organs from HCV-infected donors appeared in 2017. In the THINKER study and its continuation, 20 HCV-naïve kidney transplant recipients (KTRs) received HCV-viremic organs [41,42]. Viral transmission was observed in 100% of patients. Elbasvir/grazoprevir (EBR/GZR) was initiated as soon as viremia was detected (i.e. on average 3 days after transplantation) and continued for 12 weeks. This enabled a sustained virologic response (SVR) in all the patients, and allograft function after 6 and 12 months did not vary from that of matched recipients of HCV-negative grafts. Notably, KTRs were tested for their genotype and resistance-associated substitutions (RAS) prior to randomization, and only genotypes 1 and 4 were acceptable. Those with genotype 1 were treated using DAAs for 16 weeks, and ribavirin was added as needed (Table 1).

The EXPANDER study, in turn, utilized prophylactic DAA therapy. One dose of EBR/GZR was administered before transplantation, and the treatment was continued for 12 weeks [26]. For those with genotypes other than 1, sofosbuvir (SOF) was added to EBR/GZR. SVR was achieved in 100% of cases, and severe complications such as AR, graft loss, or liver damage were not observed (Table 1).

The possibility of shortening the treatment duration to below the standard of 12 weeks has also attracted much interest. Sise et al. conducted a study in which glecaprevir/pibrentasvir (GLE/PIB) was administered for 8 weeks starting from the second to fifth day after transplantation [37,38]. Thirty HCV-naïve patients underwent kidney transplantation from HCV-viremic donors and were followed up for a median duration of 9 months. All patients achieved SVR and acute cellular rejection (ACR) and BK viremia were observed in three patients. Durand et al. enrolled 10 patients who received GLE/PIB for 4 weeks, with the first dose being administered before transplantation. Virus transmission was observed in 50% of KTRs, and 100% SVR was observed after 12 weeks. The authors reported 100%

Table 1. KT from HCV-viremic donors to HCV-negative recipients.

Study	Genotype	Treatment strategy	Waitlist time from consent to KT	Number of KTRs	Prevalence of detected viremia in KTRs	Time to DAAs initiation	Immunosuppression	SVR	Outcomes
Sise et al. [39]	All 6 donors had 1a genotype	Single dose preoperatively + 12 weeks post-transplant: • EBZ/GPR (+RBV and 16 weeks if NS5A RAS occurred)	6.5 months	8	88%	Preemptive	Induction: • rATG 88% • Basiliximab Maintenance immunosuppression: • Tac • MMF • prednisone	100%	• Mean Cr at 6 months 1,27mg/dl • −100% patient survival • −88% graft survival • 12.5 % BKV • 37.5% DGF • 37.5% elevation in transaminases • median KDPI 31% • median VL_{peak} on POD 7was 69 IU/ml
Graham et al. [75]	Donor Genotype: • 1 3/30 • 1a 18/30 • 1/3a 1/30 • 2 1/30 • 3 4/30 • 4 1/30 • Unknown 2/30	Introduced postoperatively and continued for 12 weeks: • GLE/PIB 29/30 • SOF/VEL 1/30	1355 D	30	100%	POD 9	Induction: • Basiliximab 60% • rATG 26.7% • rATG/IVIG Maintenance immunosuppression: • Tac • MMF • prednisone	100%	• Median eGFR: 55.5 mL/min/ 1.73 m2 at 6 months • patient and graft survival were 100%, • The median follow-up of 10 months • 6,6% AR • 27% DGF • 3,3% CMV viremia • 6,6% AST and ALT > 3x the ULN. • KDPI: • UNOS allocation 62,8% • KDPI *sans* HCV 39,5% • Median VL_{peak} 3.4×10^5 copies/μL on POD 7 • Median D of viremic detection POD2 • $HCV_{Clearance}$ on POD 53
Feld et al. [36]	Donor genotypes: • 1a 7/18 • 1 b 1/18 • 2 2/18 • 3 5/18 • 2/18 unknown • unspecified 1/18	Single dose preoperatively + 7 Ds post-transplant: • Ezetimibe + GLE/PIB	KTRs were given 3-12 h prior to transplantation to sign the ICF	10 (13 lungs 6 harts 1 kidney-pancreas)	60%	preemptive		100%	• Median follow-up 36 weeks • Grade 3 ALT elevation • No AR episodes in KTRs • 100% graft and patient survival among KTRs • Median VL_{peak} on POD 1 1.87 log_{10} IU/mL
Terrault et al. PROACT [35]	Not provided	Introduced postoperatively and continued for 12 weeks: • SOF/VEL	48 D	11 KTRs	91%	POD 16.5	Induction: • rATG 82% • Basiliximab	100%	• 100% patient and graft survival • 18% DGF • 9% NASH • 18% elevation of LFTs • median KDPI 52% • median VL on POD 3 was 3.6 log_{10} IU/mL
Crismale et al. [84]	KTRs Genotypes (obtained after testing positive for HCV RNA): • 4/13 1a • 2/13 1 b	Introduced postoperatively and continued for 12 weeks: • SOF/VEL 55% • SOF/LED 27%	79 D	13	85%	POD 40	Induction: • rATG 92% • Basiliximab Maintenance immunosuppression:	100%	• -Median eGFR: 69.9 mL/ min/1,73m^2 • 100% patient and graft survival • median follow-up 8 months

(*continued*)

Table 1. Continued.

Study	Genotype	Treatment strategy	Waitlist time from consent to KT	Number of KTRs	Prevalence of detected viremia in KTRs	Time to DAAs initiation	Immunosuppression	SVR	Outcomes
	• 5/13 3	• GLE /PIB 18%					• Tac • MMF • prednisone		• 18% flu-like symptoms, fatigue, malaise • KDPI 52% • median VL at POW 1 was 56 173 IU/L • median VL at DAAs initiation was 8 661 412 IU/L
Goldberg et al. [41] Thinker	GT 1 10/10	Introduced postoperatively and continued for 12 weeks: • EBZ/GPR +/− RBV (if NS5A RAS occurred 16 weeks)	58 D	10	100%	POD 3	Induction: • rATG 92% Maintenance immunosuppression: • Tac • MMF • prednisone	100%	• Median Cr 1.1 mg/dL at 6 months, 62.8 mL/min/1.73 m2, • median follow-up 6 months • 1/10 DGF • 1/10 proteinuria due to FSGS • •2/10 transient elevation in transaminases • median KDPI 42%
Reesee et al.[42] Thinek-2	Donor GT: GT 1 100%	Introduced postoperatively and continued for 12 weeks: • EBZ/GPR (16 weeks + RBV if NS5A RAS occurred)	57 D	20	100%	POD3	Induction: • rATG Maintenance immunosuppression: • Tac • MMF • prednisone	100%	• eGFR at 6 months 67.5 mL/min/1.73 m2, at 12 months 72.8 mL/min/1.73 m2 • 3/20 developed dnDSA • 1/20 proteinuria due to FSGS • 5/20 transient elevation in transaminases (THINKER-1) • 5/20 DGF • No acute rejection episodes • Median KDPI UNOS 46%
Gupta et al.[43] **DAPPeR REFORM HEPC**	Donor Genotype available in 27/50: • 19/31 1a • 2/31 2 • 6/31 3	Pre-transplant: - SOF/VEL x 1 dose Post-transplant: - Group 1 - SOF/VEL 1 dose - Group 2 SOF/VEL 3 doses - If KTR tested positive for HCV NAT, treated with - Group 1: EBR/GZR 12 weeks (GT1) - Group 2 A: SOF/VEL +/- RBV 12 weeks (GT 2,3) - Group 2B treatment based on genotype and resistance testing	30D	50	−34% had detectable viremia post-transplant −12% required treatment • Group1 30% • Group2 3/40 7,5%(group 2 A 2/15 13%, group 2B 1/25 4%)	preemptive	Induction: • rATG Maintenance immunosuppression: • Tac • MMF • prednisone	83%	• Mean +/-(SD) eGFR: 58 mL/min/1,73m^2 • •98% patient and graft survival • Median follow-up 8 months • 2/5 required 2nd line treatment • 6th patient failed 2nd line DAA • ACR 4% • 4% transient elevation in transaminases (KTRs without viremie detected) • Dn DSA 6% • DGF 48% • KDPI mean SD: • -UNOS allocation 62+/-18 • 'optimal' 37 +/- 18
Durad et al.[26] Expander	Donor GTs: • 3/10 1a • 1/10 1a/3 • 2/10 2 • 4/10 ND	**GT 1,4 or unknown:** Pre-operative: - EBR/GZR x 1 dose Post-transplant: - EBR/GZR x 12 weeks,	1 month	10	30%	preemptive	Induction: • rATG Maintenance immunosuppression: • Tac	100%	• Median eGFR at 6 months 63.5 mL/min/1.73 m2 • (50%) anti-HCV seroconversion at 6 months • 40% DGF

(*continued*)

Table 1. Continued.

Study	Genotype	Treatment strategy	Waitlist time from consent to KT	Number of KTRs	Prevalence of detected viremia in KTRs	Time to DAAs initiation	Immunosuppression	SVR	Outcomes
		(16 weeks + RBV if NS5A RAS occurred) **GT 2,3:** Pre-operative: - EBR/GZR x 1 dose Post-transplant -EBR/GZR + SOF x 12 weeks					• MMF • prednisone		• 10% aminotransferase elevation > 5x ULN • median KDPI score 45% • Median VL was 62 400 IU/mL
Molnar et al.[47]	KTRs Genotypes: • 34/53 1a • 1/53 1 b • 3/53 2 • 15/53 3	Introduced postoperatively and continued for 12 (5 required 16) weeks: • GLR/PIB 89% • SOF/VEL 9% • SOF/LED		53	100%	76 POD	Induction: • rATG Maintenance immunosuppression: • Tac • MMF • prednisone	100%	• Mean eGFR at SVR12: 67 mL/min/1,73m^2 • 100% patient and graft survival • Median follow-up 8 months • 7,5% AR, • −16/53 DSA 30% (13% class I, 23% class II) • −18/53BK viremia 34%, • −32/53 CMV viremia • −1/53 fibrosing cholestatic hepatitis, • −19% AST, 15% ALT elevation > 3 times normal • −3/53 DGF • Mean KDPI : • UNOS allocation 51% • 'optimal' 24%
Kapila et al.[46]	Recipients' Genotypes: • 1a 38/64, • 1 b 1/64, • 1 3/64 • 2 6/64 • 3 8/64 • 4 3/64 • 1a/3 1/64 • 2/3 1/64	Introduced postoperatively and continued for 12 weeks: • GLE/PIB (60%) (1 patient received SOF/LED for 4 weeks and was transitioned to GLE/PIB for 8 additional weeks) • SOF/LED	23,5 d	64 KTRs	95% 58 of 61 started on DAA's	72 POD	Induction: • rATG Maintenance immunosuppression: • Tac • MMF • prednisone	71% • 10 undetectable HCV RNA not eligible for SVR12 • 7 remains on treatment • 1 nonresponder	• Patient survival 98% (1 patient died 77 days after transplant due to unknown cause, did not received DAAs treatment) • Median follow-up ~10 months • 2 FCH • Median KDPI: 54%
Sise et al.[37] MYTHIC	Donor GTs: • 1a 13/15 • 2 1/15 • 4 1/15	For 12 weeks Introduced postoperatively and continued for 8 weeks: • GLE/PIB	6.3 weeks	30	79%	2-5 POD	Induction • rATG 97% (one rATG + basiliximab) • no antibody induction therapy Maintenance immunosuppression (90%): • Tac • MMF • prednisone	100%	• Median eGFR at 6 months 57 mL/min/1.73 m^2 at 6 months • Median follow-up 9 months • 97% patient and graft survival 1 death attributed to sepsis 9 months post-transplant • Median KDPI 53% • 10% ACR • 10% BKV • 23% DGF • 17% proteinuria > 1 g/d

(*continued*)

Table 1. Continued.

Study	Genotype	Treatment strategy	Waitlist time from consent to KT	Number of KTRs	Prevalence of detected viremia in KTRs	Time to DAAs initiation	Immunosuppression	SVR	Outcomes
Durad et al.[38]	Donor Genotypes: • 1 a 6/10 • 1 b 1/10 • 2 2/10 • indeterminate 1/10	Single dose							• Median VL_{peak} was 2135 IU/ml preoperatively + 4 weeks post-transplant: • GLE/PIB
24 D	10	50%	preemptive		100%	• Median follow-up 12 months • Median eGFR 54.5 mL/min/1.73 m2 at POW12, • One graft failure due to venous thrombosis • 100% patient survival • No serious treatment-related adverse events were reported • No AR reported • Median KDPI 60%			
Frebius-Kardasz et al.[48]	Donor Genotypes: • 1a 2/7 • 1 b 2/7 • 3a 1/7 • Unknown 2/7	Introduced postoperatively and continued for 8/12 weeks: • SOF/LED +/- RBV • SOF/VEL		7	100%	POD 7	Induction • baziliximab (+PEX/IVIG in one patient) Maintenance immunosuppression • Tac (85%), • MMF • prednisone	100%	• Mean eGFR 63 mL/min/1.73m^2 at SVR • No AR reported • No serious treatment-related adverse events were reported • Median $VL_{peak\ was}$ 291 500 IU/mL
Forbes et al.[40]	Recipients GT: • 1a 7/12 • 1a/1b 2/12 • 3 3/12	Introduced postoperatively and continued for 12 weeks: • GLE/PIB(75%) • SOF/LED *Perioperative: • 6/12 kidneys pumped with perfusate exchange • 6/12 paired kidneys without intervention	58.7 D	12	100%	• 32 POD pumped cohort • 26 POD unpumped cohort	Induction: • Alentuzumab 92% • Basiliximab Maintenance immunosuppression: • TAC • MMF • Prednisone	50% SVR 12 (6 pending) 100% SVR4	• 100% patient survival, 92% graft survival • Median follow-up ~6.2 months • 1 AMBR resulting in graft loss (received a pumped kidney) • average KDPI 47,5% • the pumped patient cohort VL was 413 471 IU/ml /unpumped 4 360 359 IU/ml at POW 1

GT = genotype; KTR = kidney transplant recipient; rATG = rabbit antithymocyte globulin; Tac = tacrolimus; GLE/PIB = glecaprevir/pibrentasvir; HCV = hepatitis C virus; NAT = nucleic acid testing; KDPI = kidney donor profile index; MMF = mycophenolate mofetil; eGFR = glomerular filtration rate estimated, Cr = serum creatinine; SOF/LED = sofosbuvir/ledipasvir; SOF/VEL = sofosbuvir/veltapasvir; EBZ/GPR – elbasvir/grazoprevir; SVR 12 = sustained viral response 12 weeks after treatment cessation; BKV = polyoma virus viremia; DGF = delayed graft function; POD – post operating day; AR – acute rejection; ABMR – antibody-mediated rejection; TAC – tacrolimus; MMF – mycophenolate mofetil; D – day; ULN – upper limit of normal; KT = kidney transplantation; ICF = Informed Consent Form; RAV = resistance-associated variant; PEX = plasmapheresis; IVIG = intravenous immunoglobulins; ACR = acute cellular rejection.

patient survival and one graft loss attributed to vein thrombosis. However, they reported no episodes of AR [38].

Gupta et al. presented an even more aggressive strategy of limiting the time of DAA therapy after HCV NAT D+/R- transplantation [43]. In the DAPPeR study, patients received a single dose of DAAs, followed by one or three doses after transplantation. Administering two doses of DAAs resulted in an infection transmission of approximately 30%, while a 4-day protocol helped limit it to 7.5%. Only six patients required treatment, while the rest had low, self-limiting viremia. Ultimately, 83% of the treated patients achieved SVR. One patient, in whom the infection relapsed, did not achieve SVR with the first or second course of treatment. This patient did not wish to receive further treatment. Incidence of ACR and development of *de novo* donor-specific antibodies (DSA) did not exceed those observed in HCV-aviremic donors and accounted for 4% and 6% respectively (Table 1) [44,45].

The breakthrough in transplantation that occurred after the publication of the THINKER and EXPANDER study results encouraged other researchers to attempt replicating these results in 'real-life' studies. Kapila et al. presented the largest such study, which included 64 KTRs. Treatment with GLE/PIB or sofosbuvir/ledipasvir lasted 12 weeks and was initiated 72 days after transplantation. Three recipients did not develop viremia, even though the donors had low, but detectable viremia lower than 142 IU/mL. All but one patient achieved SVR. One patient did not respond to treatment because of resistance to NS5A inhibitors and was retreated with sofosbuvir/velpatasvir/voxilaprevir [46]. Fibrosing cholestatic hepatitis was observed in two patients; eleven and fourteen weeks after transplant. Both were successfully treated with DAAs.

Several other real-life and clinical studies have provided satisfactory results in treating HCV from a donor organ (Table 1) [47,48]. Promising results of HCV NAT D+/R- transplants can also be seen in case of other organs, such as the heart or lungs [49,50].

Willingness to accept HCV-viremic organs

A study by Potluri et al. showed that over the period from 2015 to 2019, the willingness to accept a seropositive organ increased sixfold [16]. However, other studies point to the fact that recipients infected with HCV are unwilling to accept an infected graft. This results in a great majority of HCV NAT+ kidneys being transplanted to HCV-naïve recipients [16]. An analysis by McCauley et al. showed that as many as 80% of patients are willing to accept an organ from an HCV NAT+ donor under certain conditions, while 18% would not accept it under any circumstance [51]. This decision is mainly influenced by the expected effectiveness of treatment, quality of the organ, and the duration of being on the organ waiting list. The above study also points to a lack of knowledge among patients about HCV infection. This underscores the need for comprehensive education programs and access to reliable data to help KTRs make an informed decision regarding HCV NAT D+/R- transplants.

Donor/recipient selection criteria

HCV NAT D+/R- transplants require careful donor and recipient selection. However, standards governing which patients could benefit from receiving an organ from an HCV NAT+ donor and which donors should be considered as potential candidates are currently lacking. Similarly, no unified regulations exist regarding the quality of organs obtained from HCV NAT+ donors.Unquestionably, patients with long anticipated waiting times should be considered for HCV NAT D+/R- transplants if this may reduce the waiting time. Their condition is likely to deteriorate, or they may die, until an organ becomes available; hence, HCV NAT D+/R- transplantation confers a survival benefit to these patients. Moreover, for these patients, remaining on the waitlist may constitute a greater risk than being infected with HCV that may be successfully treated in great majority of cases.

A survey by Lentine et al. showed that HCV-naïve patients with cirrhosis or a history of liver disease are not offered HCV-viremic organs [18]. However, even individuals without already diagnosed liver diseases are at risk. More than half of the patients awaiting kidney transplantation are diabetic or prediabetic; similarly, the impact of obesity in this population is higher than that in the general population [52]. Both diabetes mellitus and obesity, which are components of metabolic syndrome, may affect liver function. This is reflected by the greater NAFLD prevalence in these populations, which may exceed 50% [53]. Patients with NAFLD may exhibit normal liver enzymes and remain asymptomatic; therefore, they often remain undiagnosed. Offering HCV-viremic organs to patients who are likely to have undiagnosed liver disease poses a threat of progression of liver disease, including hepatocellular carcinoma, which has been observed even in patients with NAFLD without evidence of cirrhosis [54]. Furthermore, KTRs with diabetes and obesity, as well as undiagnosed liver conditions, who receive organs from HCV NAT+ donors

face a greater risk of metabolic complications, resulting in a higher risk of mortality [55]. Importantly, screening for NAFLD is not recommended in the general population and approaches to screening in high-risk patients vary across guidelines and is not recommended by the American Association for the Study of Liver Disease (AASLD) [56–58]. Therefore, the implementation of FibroScan in standard recipient evaluation prior to HCV NAT D+/R- transplantation could facilitate proper recipient selection.

A strong positive correlation has been reported between RNA levels in organ donors and recipients [41]. Despite this, donor HCV viremia is not routinely reported. Knowledge of viral load could enable identification of individuals at higher risk of HCV-related complications and determination of optimal timing of DAA therapy initiation.

Patients requiring nonstandard immunosuppression or desensitization therapy are frequently excluded from HCV NAT D+/R- protocols. Drug–drug interactions between immunosuppressive agents and DAAs may also translate to underimmunosuppression or decreased efficacy of DAA therapy. Recent experience shows that this may be mitigated by early initiation of pangenotypic treatment. Pangenotypic DAA regimens have limited drug–drug interactions with tacrolimus and may limit the need to adjust the dose of calcineurin inhibitors, even though tacrolimus levels have to be monitored. The lack of reduction in tacrolimus levels mitigates the risk of underimmunosuppression, and hence the risk of *de novo* DSA development and AR. Nevertheless, it is still essential to identify patients at a high risk of AR, such as highly sensitized patients or those requiring retransplantation, and to carefully weigh the risks and benefits of selecting HCV NAT D+/R- organs.

Although the donor genotype and the presence of RAS might be of great importance in patients who are known to be treatment-experienced, they are mainly not known prior to transplantation. Therefore, excluding donors who were previously treated with NS5 inhibitors or those who have relapsed seems a reasonable mean to avoid difficulties in viral clearance after transplantation and a situation when no antiviral treatment will be available for the patient. However, the history of antiviral treatment is often unknown before transplantation.

The donor's genotype is crucial if there is no access to pangenotypic antiviral agents. However, in the case of pangenotypic drugs, there is still the issue of RAS in relation to NS5A protease inhibitors, especially in genotypes 1a and 3, which can result in prolonged treatment and a worse treatment result [59]. Contrary to the resistance to NS3-4A protease inhibitors, which resolves in a few weeks or months, the resistance to NS5 protease inhibitors can last for a year and can influence the results of recurrent treatment. Importantly, genotypes 1a and 3 are more often seen in PHS criteria increased risk donors, and this fact is often unknown before transplantation [60]. Studies have estimated that up to 4% of patients require changes in DAA therapy [61,62]. Moreover, in some cases, both the first and second lines of treatment did not allow the patient to achieve SVR. However, the American Society of Transplant Surgeons, in its consensus, stated that a lack of knowledge of the genotype or the presence of RAS should not be a contraindication for HCV NAT D+/R- kidney transplantation, provided that treatment can be initiated without delay [12].

Patients who are predicted not to comply with procedures, DAA schedule, and surveillance requirements after transplant should also not be offered HCV-viremic organs. Education of patients potentially willing to accept HCV-viremic organs could promote compliance with posttransplant DAA therapy. A unified policy regarding donor and recipient selection for HCV NAT D+/R- transplantation could encourage broader utilization of HCV NAT + organs.

DAAs

HCV therapy involves a combination of two or three DAAs that target nonstructural proteins of the HCV and may be delivered with little adverse effect and high efficacy. Pangenotypic DAAs are preferred. The only drawbacks are accessibility to DAAs and the high cost of DAA therapy.

The AASLD and Infectious Diseases Society of America (IDSA) recommend GLE/PIB for 8 weeks or SOF/VEL for 12 weeks for the treatment of HCV-naïve recipients of HCV-viremic organs other than the liver. However, multiple factors should be considered before initiating DAA therapy, especially if pangenotypic agents are unavailable; these factors include any evidence of liver dysfunction, concomitant medications, and to a lesser extent immunosuppression that will be used after transplantation.

Drug-drug interactions must also be accounted for in the DAA therapy selection process to avoid complications, because premature withdrawal of DAA therapy increases the development of drug resistance. Studies have estimated that up to 45% of patients may require an adjustment of the dosage of the calcineurin inhibitor during DAA therapy [63,64]. Another example is

patients who require antiepileptic treatment in the period near transplantation, as antiepileptic drugs are not recommended to be taken together with any DAA. A similar situation occurs in the case of high doses of proton pump inhibitors (PPIs; taken twice daily), such as ledipasvir, and this can negatively influence the effectiveness of DAA therapy. However, standard doses of PPIs (corresponding to 20 mg of omeprazole) can be used without adverse events. A great tool facilitating assessment of drug-drug interactions is interaction checker available on https://www.hep-druginteractions.org/checker.

Treatment should also consider the path of drug elimination and kidney function, but this has been subject to change recently. The AASLD/IDSA guidelines have been drafted such that when applying the recommended schemas of treatment for individual patient groups, the dosage need not be adjusted in the case of patients with chronic kidney disease (CKD) or those receiving dialysis[63]. SOF, which is effective in treating genotype 3, is mainly renally excreted. Therefore, it was not recommended for patients with CKD and an estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73 m^2, but it was approved in November 2019 by the US Food and Drug Administration for use in patients with an eGFR below 30 mL/min/1.73 m^2 and those who were dialysis-dependent [63].

Optimal timing of DAA initiation

Currently, there is little doubt that antiviral treatment in HCV NAT + patients can be postponed until after transplantation, in order to allow them to receive a kidney from a donor infected with HCV. However, the optimal time for introducing treatment in such cases of virus transmission from the donor has not yet been established. The new AASLD/IDSA guidelines suggest the initiation of prophylactic treatment or preemptive treatment latest by 7 days after transplantation [63].

Recent studies have adopted various approaches for the introduction of antiviral treatments. Durand et al. in their study began treatment before transplantation, while in the THINKER study, DAAs were introduced after HCV viremia was detected [26,41,42]. Some centers postpone treatment for a couple of weeks until the patient and immunosuppressive treatment are stable enough to avoid the need for early DAA therapy withdrawal. In the study by Molnar et al., DAA therapy was introduced on average 76 days after transplantation [47]. The authors do not claim that this was the intentional time of introducing the treatment, but rather a result of difficulties in obtaining approval for treatment costs from the insurers. This resulted in complications such as fibrosing cholestatic hepatitis or AR. Moreover, higher than expected incidence rate of CMV viremia and BK viremia were observed. However, a national registry-based study by Yazawa et al. did not prove the association between donor-derived HCV viremia and CMV viremia, whereas the more recent study by Molnar et al. found that KTRs undergoing HCV NAT D+/R- transplant may be at increased risk of developing high-level BK viremia [65,66]. In the THINKER and EXPANDER studies, no serious complications were observed in the early posttransplant period [26,41,42]. A recent survey conducted by Lentine et al. showed that the majority of transplant centers initiated DAA therapy after HCV viremia was detected and after hospital discharge [18].

Postponing treatment for a few months may be associated with serious complications. An acute infection with HCV has been associated with the development of fulminant hepatitis or fibrosing cholestatic hepatitis [67]. By intentionally infecting a recipient with HCV, we also risk the development of thrombotic microangiopathy and a series of immunological complications, such as AR or glomerulonephritis (GN) [68]. Studies have reported the development of GN on the 18th day after liver transplantation from a donor with an active HCV infection as well as renal failure requiring dialysis owing to delayed DAA therapy resulting from problems with acquiring approval from the insurance company [69]. The KDIGO recommends, among other things, monitoring proteinuria every 6 months in patients infected with HCV after transplantation, and performing a biopsy if HCV infection occurs. Confirmation of a relapse in the development of *de novo* GN is an indicator of immediate DAA therapy [11]. Despite this, in HCV NAT D+/R- transplantations antiviral treatment initiation in the peri-transplant period deems advisable.

Early introduction of treatment can also limit the exposure to viremia and the development of complications. Patients who start receiving treatment on call to operating room develop viremia less frequently; this decreases the risk for the recipient and, as studies show, allows shortening the duration of DAA therapy and lowering treatment costs [26,41]. In studies that utilized a prophylactic approach rather than initiating treatment after viremia detection, fewer AR episodes were observed. However, the sample size of these studies was small, and further studies are warranted to confirm these findings. On the other hand, prophylactic DAA therapy can expose patients to treatment that they may not require.

Apart from selecting the appropriate time to introduce treatment, the optimum treatment duration after transplantation is also a subject of debate. Many different strategies have been adopted in recent studies. The standard 12- to 16-week treatment duration allowed the achievement of SVR in 100% of patients under both prophylactic and reactive approaches (after HCV viremia is documented) [26,41,42]. Feld et al. enrolled 30 solid organ transplant recipients, including 10 KTRs, and started treatment with GLE/PIB in conjunction with ezetimibe (an HCV entry inhibitor) before transplantation and continued it for 7 days. This allowed for viral transmission of 67%; however, it remained unclear if viral transmission was prevented or cleared rapidly. Nevertheless, SVR was achieved in all patients [36]. Attempts to shorten the treatment period before transplantation and administering only one or two additional doses after transplantation were less than satisfactory [43]. The first-line treatment allowed only 50% of the patients to achieve SVR. Therefore, short-term DAA therapy is currently not recommended outside of clinical trials owing to insufficient data [63].

Immunosuppression

The optimal immunosuppression scheme for transplants from an HCV NAT + donor to a naïve recipient remains to be determined. An analysis by Bae et al. showed that KTRs infected with HCV have a 20% lower probability of receiving a less effective inductive treatment with interleukin 2 receptor antagonists rather than with anti-thymocyte globulin [70,71], despite HCV infection being a well-recognized factor that increases the risk of AR. This can be partly related to the clinicians' fear of overimmunosuppression in patients with HCV infection. Immunosuppressive drugs are known to have a permissive effect on HCV replication. Recent studies have shown that patients infected with HCV should receive standard immunosuppression and that depletive induction should not be avoided if there are reasons to introduce it. A retrospective analysis by Luan et al. based on data from the OPTN/Scientific Registry of Transplant Recipients showed that the type of calcineurin inhibitor (cyclosporine vs. tacrolimus) used in maintenance immunosuppression does not influence the mortality rate in patients with HCV Ab+ [72]. These data are from a period when the categorization of HCV Ab+/NAT- and HCV Ab+/NAT + donors was not possible, and the use of mycophenolate mofetil in the same analysis was related to a lower mortality rate (hazard ratio, 0.77; 95% confidence interval, 0.64-0.92; $p = 0.005$) [72].

Non-pangenotypic DAAs impact calcineurin inhibitors trough level; hence pose a risk of underimmunosuppression. Pangonotypic DAAs significantly mitigate this risk. When GLE/PIB is used, for instance, no tacrolimus dose adjustment is required prior to therapy administration; however, the tacrolimus level needs to be monitored.

KDPI calculation

In the US, the KDPI is used to estimate the expected organ survival rate after transplantation. Many factors are taken into account, including the presence of anti-HCV antibodies, which in turn often leads to an artificial increase in the KDPI by 0.25 on average in comparison to the actual quality of the organ [16,73,74]. This can lead to improper allocation of organs, which is why the issue of removing anti-HCV antibodies from the KDPI assessment has been advocated in some studies. The Kidney Allocation System (KAS) introduced in 2014, which is based on the KDPI, is supposed to better match the quality of the organ to the predicted survival of the recipient. It assumes that an organ with a KDPI of 20% should be transplanted to a recipient with an estimated posttransplant survival score of 20%. However, as a result of the overestimation of the KDPI, the KAS cannot function in accordance with its original goal. Moreover, some donors are classified as having marginal organ quality (KDPI $>$ 85%), while in reality, the quality of their organ is much better [74].

The excellent quality of organs from donors infected with HCV has been proven by Goldberg et al. and Durand et al., who reported KDPI values of 42–45% [26,41]. The analysis by Graham et al. (DAPPeR study) showed a noteworthy difference between the KDPI calculated according to the standard formula and the 'optimal' one obtained after removing the anti-HCV antibodies from the calculation (Table 1) [43,75]. With higher index values, the kidneys will be transplanted into recipients with a shorter expected survival. As HCV Ab+/NAT- donors do not constitute a risk of HCV transmission, their KDPI should not be calculated on the basis of the serological status of HCV, and this has been proven by studies that showed a comparable eGFR 6 months after transplantation, which is considered an indicator of the long-term survival of a transplant [76,77].

Informed consent

The regulations introduced by the OPTN/UNOS require informed consent from the recipient deciding to accept

a kidney from a PHS criteria donor. The acceptance of an HCV NAT + organ by an HCV-negative recipient should be preceded by a comprehensive education process, including information on the benefits and risks of such a solution.

The patient needs to be informed that the data regarding the utilization of HCV NAT + organs in HCV-negative recipients is still limited, and that current data are based on studies conducted on small populations. The long-term effects of these transplants are also unknown. The potential recipient should also be provided information on the eventualities of such a transplantation, such as the shorter time of waiting for an organ, shorter time of dialysis, and the resultant lower mortality rate, as well as potential difficulties, virus transmission paths, risk of transmission to family members, possible complications related to virus replication, and the necessity of undergoing antiviral treatment after transplantation. Owing to the relatively high cost of DAA therapy, the patient's insurance also needs to be verified to ensure it covers the treatment cost. The patient needs to be given ample amount of time to consult with other specialists or family and to formulate questions and obtain answers.

The newest PHS guidelines suggest that the consent to an organ from an HCV NAT + donor should not be on a separate form, as it currently is, but it should rather be included in the standard form of consent for an organ transplantation [34].

HCV-viremic organ refusal

Given the ever-growing demand for organs that is hard to satisfy, HCV NAT D+/R- transplants may be lifesaving in certain circumstances, despite the inherent risk associated with this practice. This is because despite the imbalance between the demand and supply of kidneys available for transplantation, hundreds of HCV-viremic kidneys are discarded annually [10].

Denying to accept an HCV NAT + organ or not being offered one entails certain consequences, particularly in transplant centers with long waiting times. Compared to accepting an HCV-viremic graft, awaiting an HCV-negative graft may imply a longer waiting time of 12 months [16]. Receiving a graft earlier usually results in a survival benefit and improved quality of life when compared to receiving an HCV-negative graft [78–80]. Most patients awaiting kidney transplantation are dialysis dependent. The time on dialysis increases the risk of death and complications leading to health deterioration [81]. As a consequence of long waiting times, more than a quarter of patients on the waiting list may die while awaiting kidney transplantation, and a proportion of patients will become too sick to qualify for transplantation [82]. Hence, it is important to state it clearly to the patients that they may not survive until they are offered an HCV-negative graft.

Furthermore, the risk of complications may be partly compensated for by a better quality of organ from a younger PHS criteria donor. Potluri et al. in their analysis showed that the kidney function of recipients from HCV NAT + and HCV Ab+/NAT- donors a year after kidney transplantation was comparable to that of recipients of HCV-negative kidneys, despite the worse KDPI in the former group [16].

Utilization of HCV-viremic kidneys increases the total number of transplantations and results in a shorter waiting time for individuals remaining on the waiting list.

Insurance

Coverage of cost of DAA therapy remains a significant concern for both patients and health care providers and prevents HCV-viremic organs from being fully utilized. As a part of clinical studies, antiviral treatment is provided by pharmaceutical companies, while in real-life scenarios, the costs have to be covered by the patient or their insurance. Data show that the percentage of refusals of requests to cover medical treatment costs, depending on the study, ranges from 20% to 35% and is more common with a public insurer than with a private one [47]. In all cases, a delayed start of treatment should be considered. Insurance companies explain their reason for rejection as the intentional transmission of the virus or the off-label usage of DAAs, as DAAs are registered only for treating chronic hepatitis C; hence, in this case, the patients have to deal with an acute infection for the first 6 months. In addition, some insurance companies require the documentation of viremia, which is not detectable at the time treatment should be initiated before transplantation, and this can result in a refusal to cover the treatment cost. In the case of a nonimmunocompetent patient, the prolonged time before starting treatment can have catastrophic results. Therefore, some authors think that in the absence of an assurance that medical treatment costs will be covered and given the possibility that patients may not be able to personally cover the treatment costs, such solutions should not be considered.

Cost-effectiveness

The utilization of organs with active HCV viremia is associated with high costs. However, keeping patients

on the waiting list is also costly in terms of the need for dialysis or the use of devices aiding cardiac function. The latest analyses show that transplanting HCV NAT + kidneys to HCV-negative recipients can be cost-effective because it could shorten the waiting time by 2 years; however, other analyses show that this period is 11 months [3,83]. It seems that the cost of DAAs will decrease and shortening the duration of DAA therapy will allow an additional reduction in the cost and availability of such treatments.

Conclusions

It is rational to prioritize the utilization of HCV NAT + organs in recipients already infected with HCV. This entails lower costs, limits the risk of possible complications, and seems more reasonable from an ethical standpoint. Such organs should be offered to HCV-negative recipients only as a secondary choice. However, this is not always possible in everyday practice.

In light of the current knowledge, the transplantation of HCV NAT + kidneys to naïve recipients may constitute a solution to organ shortage. However, such practice entails a risk of complications, especially when combined with the difficulty in providing DAA therapy in the direct posttransplant period and the need for careful donor and recipient selection. Every effort should be made to ensure DAA therapy and reduce the mortality of patients awaiting kidney transplantation.

Extended education programs should also be implemented to increase awareness of HCV infection and HCV NAT D+/R- kidney transplantation among candidates. This may encourage the acceptance of HCV-viremic organs and simultaneously maximize compliance and mitigate the risks associated with this procedure. Currently, it seems premature to utilize HCV NAT D+/R- kidney transplantation as a standard of care. Further studies are required to draw solid conclusions regarding the long-term consequences of adopting such a treatment approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

[1] Organ Procurement and Transplantation Network [accessed May 4, 2021]. Available from: http://optn.transplant.hrsa.gov.
[2] Tong J, Liu M, Li H, et al. Mortality and associated risk factors in dialysis patients with cardiovascular disease. Kidney Blood Press Res. 2016;41(4):479–487.
[3] Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2017 annual data report: kidney. Am J Transplant. 2019;19:19–123.
[4] Reese PP, Harhay MN, Abt PL, et al. New solutions to reduce discard of kidneys donated for transplantation. J Am Soc Nephrol. 2016;27(4):973–980.
[5] Rudd RA, Seth P, David F, et al. Increases in drug and Opioid-Involved overdose deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445–1452.
[6] Pruett TL, Clark MA, Taranto SE. Deceased organ donors and PHS risk identification. Transplantation. 2017;101(7):1670–1678.
[7] Bowring MG, Holscher CM, Zhou S, et al. Turn down for what? Patient outcomes associated with declining increased infectious risk kidneys. Am J Transplant. 2018;18(3):617–624.
[8] Croome KP, Lee DD, Pungpapong S, et al. What are the outcomes of declining a public health service increased risk liver donor for patients on the liver transplant waiting list? Liver Transpl. 2018;24(4):497–504.
[9] Fleetwood VA, Lusciks J, Poirier J, et al. Utilization of public health service increased risk donors yields equivalent outcomes in liver transplantation. J Transplant. 2016;2016:1–7.
[10] Reese PP, Abt PL, Blumberg EA, et al. Transplanting hepatitis C–positive kidneys. N Engl J Med. 2015;373(4):303–305.
[11] Jadoul M, Berenguer MC, Doss W, et al. Executive summary of the 2018 KDIGO hepatitis C in CKD guideline: welcoming advances in evaluation and management. Kidney Int. 2018;94(4):663–673.
[12] Levitsky J, Formica RN, Bloom RD, et al. The American society of transplantation consensus conference on the use of hepatitis C viremic donors in solid organ transplantation. Am J Transplant. 2017;17(11):2790–2802.
[13] Kucirka LM, Singer AL, Ros RL, Montgomery RA, et al. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipients. Am J Transplant. 2010;10(5):1238–1246.
[14] Trotter PB, Summers DM, Ushiro-Lumb I, et al. Use of organs from hepatitis C virus-positive donors for uninfected recipients. Transplantation. 2018;102(4):664–672.
[15] La Hoz RM, Sandıkçı B, Ariyamuthu VK, et al. Short-term outcomes of deceased donor renal transplants of HCV uninfected recipients from HCV seropositive nonviremic donors and viremic donors in the era of direct-acting antivirals. Am J Transplant. 2019;19(11):3058–3070.
[16] Potluri VS, Goldberg DS, Mohan S, et al. National trends in utilization and 1-Year outcomes with

transplantation of HCV-Viremic kidneys. J Am Soc Nephrol. 2019;30(10):1939–1951.
[17] Chang S-H, Merzkani M, Lentine KL, et al. Trends in discard of kidneys from hepatitis C viremic donors in the United States. Clin J Am Soc Nephrol. 2021;16(2): 251–261.
[18] Lentine KL, Peipert JD, Alhamad T, et al. Survey of clinician opinions on kidney transplantation from hepatitis C virus positive donors: identifying and overcoming barriers. Kidney360. 2020;1(11):1291–1299.
[19] Anderson B, Jezewski E, Sela N, et al. Public health service increased risk donor kidney grafts for transplant into children, a survey of pediatric nephrologists. Pediatr Transplant. 2021;25(2):e13863.
[20] Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B Virus-Positive donors: consensus guidelines for recipient management. Am J Transplant. 2015;15(5):1162–1172.
[21] Arthurs SK, Eid AJ, Pedersen RA, et al. Delayed-Onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. Clin Infect Dis. 2008;46(6):840–846.
[22] Bowring MG, Shaffer AA, Massie AB, et al. Center-level trends in utilization of HCV-exposed donors for HCV-uninfected kidney and liver transplant recipients in the United States. Am J Transplant. 2019;19(8): 2329–2341.
[23] Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance1 1The bundesministerium für bildung und forschung and the european union, as sponsors of the study, had no role in study design, data collection, analysis, or interpret. Gastroenterology. 2003;125(1):80–88.
[24] Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection. JAMA. 2000; 284(4):450–456.
[25] Kling CE, Perkins JD, Landis CS, et al. Utilization of organs from donors according to hepatitis C antibody and nucleic acid testing status: time for change. Am J Transplant. 2017;17(11):2863–2868.
[26] Durand CM, Bowring MG, Brown DM, et al. Direct-acting antiviral prophylaxis in kidney transplantation from hepatitis C virus–infected donors to noninfected recipients. Ann Intern Med. 2018;168(8):533.
[27] Gupta G, Kang L, Yu JW, et al. Long-term outcomes and transmission rates in hepatitis C virus-positive donor to hepatitis C virus-negative kidney transplant recipients: analysis of United States national data. Clin Transplant. 2017;31(10):e13055.
[28] Kwong AJ, Wall A, Melcher M, et al. Liver transplantation for hepatitis C virus (HCV) non-viremic recipients with HCV viremic donors. Am J Transplant. 2019;19(5): 1380–1387.
[29] Cypel M, Feld JJ, Galasso M, et al. Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. Lancet Respir Med. 2020;8(2).
[30] Bethea ED, Gaj K, Gustafson JL, et al. Pre-emptive pangenotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative heart transplantation: an open-label study. Lancet Gastroenterol Hepatol. 2019;4(10):771–780.
[31] Schlendorf KH, Zalawadiya S, Shah AS, et al. Early outcomes using hepatitis C–positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies. J Hear Lung Transplant. 2018; 37(6).
[32] Kucirka LM, Sarathy H, Govindan P, et al. Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. Am J Transplant. 2011;11(6):763–769.
[33] Suryaprasad A, Basavaraju SV, Hocevar SN, et al. Transmission of hepatitis C virus from organ donors despite nucleic acid test screening. Am J Transplant. 2015;15(7):1827–1835.
[34] Jones JM, Kracalik I, Levi ME, et al. Assessing solid organ donors and monitoring transplant recipients for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection — U.S. Public health service guideline, 2020. MMWR Recomm Reports. 2020;69(4): 1–16.
[35] Terrault NA, Burton J, Ghobrial M, et al. Prospective multicenter study of early antiviral therapy in liver and kidney transplant recipients of HCV-viremic donors. Hepatology. 2021;73(6):2110–2123.
[36] Feld JJ, Cypel M, Kumar D, et al. Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-Centre, open-label study. Lancet Gastroenterol Hepatol. 2020;5(7).
[37] Sise ME, Goldberg DS, Kort JJ, et al. Multicenter study to transplant hepatitis C–infected kidneys (MYTHIC): an open-label study of combined glecaprevir and pibrentasvir to treat recipients of transplanted kidneys from deceased donors with hepatitis C virus infection. J Am Soc Nephrol. 2020;31(11):2678–2687.
[38] Durand CM, Barnaba B, Yu S, et al. Four-week direct-acting antiviral prophylaxis for kidney transplantation from hepatitis C–viremic donors to hepatitis C–negative recipients: an open-label nonrandomized study. Ann Intern Med. 2021;174(1):137–138.
[39] Sise ME, Strohbehn IA, Chute DF, et al. Preemptive treatment with elbasvir and grazoprevir for hepatitis C–viremic donor to uninfected recipient kidney transplantation. Kidney Int Reports. 2020;5(4):459–467.
[40] Forbes RC, Concepcion BP, Clapper D, et al. The effect of pulsatile pump perfusion on hepatitis C transmission in kidney transplantation: a prospective pilot study. Clin Transplant. 2020;34(8):e13987.
[41] Goldberg DS, Abt PL, Blumberg EA, et al. Trial of transplantation of HCV-Infected kidneys into uninfected recipients. N Engl J Med. 2017;376(24): 2394–2395.
[42] Reese PP, Abt PL, Blumberg EA, et al. Twelve-month outcomes after transplant of hepatitis C–infected kidneys into uninfected recipients. Ann Intern Med. 2018; 169(5):273–281.
[43] Gupta G, Yakubu I, Bhati CS, et al. Ultra-short duration direct acting antiviral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis C negative kidney transplant recipients. Am J Transplant. 2020;20(3):739–751.

[44] Lionaki S, Panagiotellis K, Iniotaki A, et al. Incidence and clinical significance of *de novo* donor specific antibodies after kidney transplantation. Clin Dev Immunol. 2013;2013:849835.
[45] Cooper JE. Evaluation and treatment of acute rejection in kidney allografts. Clin J Am Soc Nephrol. 2020; 15(3):430–438.
[46] Kapila N, Menon KVN, Al-Khalloufi K, et al. Hepatitis C virus NAT-positive solid organ allografts transplanted into hepatitis C virus–negative recipients: a real-world experience. Hepatology. 2020;72(1):32–41.
[47] Molnar MZ, Nair S, Cseprekal O, et al. Transplantation of kidneys from hepatitis C–infected donors to hepatitis C–negative recipients: single center experience. Am J Transplant. 2019;19(11):3046–3057.
[48] Friebus-Kardash J, Gäckler A, Kribben A, et al. Successful early sofosbuvir-based antiviral treatment after transplantation of kidneys from HCV-viremic donors into HCV-negative recipients. Transpl Infect Dis. 2019;21(5):e13146.
[49] McLean RC, Reese PP, Acker M, et al. Transplanting hepatitis C virus–infected hearts into uninfected recipients: a single-arm trial. Am J Transplant. 2019;19(9): 2533–2542.
[50] Woolley AE, Singh SK, Goldberg HJ, et al. Heart and lung transplants from HCV-Infected donors to uninfected recipients. N Engl J Med. 2019;380(17): 1606–1617.
[51] McCauley M, Mussell A, Goldberg D, et al. Race, risk, and willingness of end-stage renal disease patients without hepatitis C virus to accept an HCV-Infected kidney transplant. Transplantation. 2018;102(4): e163–e170.
[52] Guthoff M, Vosseler D, Langanke J, et al. Diabetes mellitus and prediabetes on kidney transplant waiting List- Prevalence, metabolic phenotyping and risk stratification approach. PLoS One. 2015;10(9): e0134971.
[53] Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Transl Gastroenterol Hepatol. 2020;5:16–16.
[54] Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2016;14(1):124–131.
[55] Mikolasevic I, Racki S, Zaputovic L, et al. Nonalcoholic fatty liver disease (NAFLD) and cardiovascular risk in renal transplant recipients. Kidney Blood Press Res. 2014;39(4):308–314.
[56] European Association for the Study of The Liver, & European Association for the Study of Diabetes. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388–1402.
[57] LaBrecque DR, Abbas Z, Anania F, et al. World gastroenterology organisation global guidelines. J Clin Gastroenterol. 2014;48(6):467–473.
[58] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology. 2018;67(1): 328–357.
[59] Poordad F, Pol S, Asatryan A, et al. Glecaprevir/pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. Hepatology. 2018;67(4):1253–1260.
[60] Robaeys G, Bielen R, Azar DG, et al. Global genotype distribution of hepatitis C viral infection among people who inject drugs. J Hepatol. 2016;65(6):1094–1103.
[61] Sawinski D, Patel N, Appolo B, et al. Use of HCV + donors does not affect HCV clearance with directly acting antiviral therapy but shortens the wait time to kidney transplantation. Transplantation. 2017; 101(5):968–973.
[62] Lin MV, Sise ME, Pavlakis M, et al. Efficacy and safety of direct acting antivirals in kidney transplant recipients with chronic hepatitis C virus infection. PLoS One. 2016;11(7):e0158431.
[63] Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American association for the study of liver diseases–infectious diseases society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology. 2020;71(2):686–721.
[64] Sawinski D, Kaur N, Ajeti A, et al. Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. Am J Transplant. 2016; 16(5):1588–1595.
[65] Yazawa M, Fülöp T, Cseprekal O, et al. The incidence of cytomegalovirus infection after deceased-donor kidney transplantation from hepatitis-C antibody positive donors to hepatitis-C antibody negative recipients. Ren Fail. 2020;42(1):1083–1092.
[66] Molnar MZ, Potluri VS, Schaubel DE, et al. Association of donor hepatitis C virus infection status and risk of BK polyomavirus viremia after kidney transplantation. Am J Transplant. 2021;22(2):599–609.
[67] Kapila N, Al-Khalloufi K, Bejarano PA, et al. Fibrosing cholestatic hepatitis after kidney transplantation from HCV-viremic donors to HCV-negative recipients: a unique complication in the DAA era. Am J Transplant. 2020;20(2):600–605.
[68] Baid-Agrawal S, Farris AB, Pascual M, et al. Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy. Kidney Int. 2011;80(8): 879–885.
[69] Wadei HM, Pungpapong S, Cortese C, et al. Transplantation of HCV-infected organs into uninfected recipients: advance with caution. Am J Transplant. 2019;19(3):960–961.
[70] Bae S, Durand CM, Garonzik-Wang JM, et al. Antithymocyte globulin versus interleukin-2 receptor antagonist in kidney transplant recipients with hepatitis C virus. Transplantation. 2020;104(6):1294–1303.
[71] Baid S, Cosimi AB, Tolkoff-Rubin N, et al. Renal disease associated with hepatitis C infection after kidney and liver transplantation1, transplantation. Transplantation. 2000;70(2):255–261.
[72] Luan FL, Schaubel DE, Zhang H, et al. Impact of immunosuppressive regimen on survival of kidney transplant recipients with hepatitis C. Transplantation. 2008;85(11):1601–1606.

[73] Amundsen B, Sise M, Lin M, et al. Utilization of HCV-positive donors' kidneys: potential benefits in the era of direct acting antiviral (DAA) therapy: abstract# P-92. Am J Transplant. 2016;16.
[74] Sibulesky L, Kling CE, Blosser C, et al. Are we underestimating the quality of aviremic hepatitis C-positive kidneys? Time to reconsider. Am J Transplant. 2018; 18(10):2465–2472.
[75] Graham JA, Torabi J, Ajaimy M, et al. Transplantation of viral-positive hepatitis C-positive kidneys into uninfected recipients offers an opportunity to increase organ access. Clin Transplant. 2020;34(4):e13833.
[76] Yazawa M, Balaraman V, Tsujita M, et al. Donor hepatitis C antibody positivity misclassifies kidney donor profile index in non-hepatitis C-infected donors: time to revise the kidney donor profile index – a retrospective cohort study. Transpl Int. 2020;33(12):1732–1744.
[77] Keith D, Hishio Lucar A, Vranic G. The relationship between kidney donor profile index and six month eGFR in deceased donor recipients. Am J Transplant. 2016;16(Suppl(398) [abstract #560]).
[78] Sawinski D, Forde KA, Lo Re V, et al. Mortality and kidney transplantation outcomes among hepatitis C virus–seropositive maintenance dialysis patients: a retrospective cohort study. Am J Kidney Dis. 2019; 73(6):815–826.
[79] Abbott KC, Lentine KL, Bucci JR, et al. The impact of transplantation with deceased donor hepatitis C-positive kidneys on survival in wait-listed long-term dialysis patients. Am J Transplant. 2004;4(12):2032–2037.
[80] Bloom RD, Sayer G, Fa K, et al. Outcome of hepatitis C Virus-Infected kidney transplant candidates who remain on the waiting list. Am J Transplant. 2005;5(1): 139–144.
[81] Wolfe RA, McCullough KP, Schaubel DE, et al. Calculating life years from transplant (LYFT): methods for kidney and kidney-pancreas candidates. Am J Transplant. 2008;8(4p2):997–1011.
[82] Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 annual data report: kidney. Am J Transplant. 2017;17: 21–116.
[83] Kadatz M, Klarenbach S, Gill J, et al. Cost-effectiveness of using kidneys from hepatitis C nucleic acid test-positive donors for transplantation in hepatitis C-negative recipients. Am J Transplant. 2018;18(10): 2457–2464.
[84] Crismale JF, Khalid M, Bhansali A, Boccardo G, Khaim R, Florman SS, et al. Liver, simultaneous liver-kidney, and kidney transplantation from hepatitis C-positive donors in hepatitis C-negative recipients: A single-center study. Clin Transplant. 2020;34(1).

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Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey

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Abstract: Chronic hepatitis C (CHC) is prevalent in the hemodialysis-dependent population. Currently, all patients with CHC should be considered for treatment; however, many hemodialysis-dependent patients are still left untreated. Following HCV cure, accurate surveillance is mandatory to reduce liver-related mortality and prevent reinfection. We aimed to establish HCV management practices and barriers to HCV elimination in dialysis centers in Poland. Polish dialysis centers were surveyed via email. The HCV management strategies were investigated. Representatives of 112 dialysis centers responded, representing 43.1% of all dialysis centers in Poland and 43.4% of hemodialysis-dependent patients' volume. Most respondents were Heads of hemodialysis centers and board-certified nephrologists. The study demonstrated that in the vast majority of hemodialysis centers (91.6%), subjects are considered for antiviral treatment (AVT); however, many obstacles preventing patients from being prescribed AVT were identified; patients' reluctance to undergo AVT was most reported (60%). The majority of dialysis units neither evaluate patients with CHC for liver fibrosis (60.4%) nor screen them for hepatocellular carcinoma (53.5%). In conclusion, the presented study demonstrates that HCV management practices across Polish dialysis centers vary substantially. There is a need to optimize and streamline the HCV management infrastructure in the hemodialysis population in Poland.

Keywords: hepatitis C virus (HCV); eradication of infection; Direct Acting Antivirals (DAA)

Citation: Czarnecka, P.; Czarnecka, K.; Tronina, O.; Baczkowska, T.; Zarychta-Wisniewska, W.; Durlik, M. Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey. *J. Clin. Med.* **2023**, *12*, 2711. https://doi.org/10.3390/jcm12072711

Academic Editors: Nadia Marascio and Giovanni Matera

Received: 15 March 2023
Revised: 2 April 2023
Accepted: 3 April 2023
Published: 4 April 2023

1. Introduction

Chronic hepatitis C (CHC) is a major health concern globally, affecting 71 million people worldwide and 140,000 patients in Poland, significantly contributing to liver-related mortality [1–4]. Now that effective antiviral treatment (AVT) is available, a CHC eradication target was set by the World Health Organization (WHO): they proposed that along with a reduction of the rate of new infections, hepatitis C virus (HCV)-related mortality is to be reduced by 65% [5]. Viral eradication has been previously demonstrated with smallpox, which was made feasible through a mass vaccination campaign. Given the lack of an HCV vaccine, this goal may be pursued only with a comprehensive approach toward HCV elimination.

The WHO's aim was to achieve macro-elimination via micro-elimination, which is less complex and more cost-effective. Micro-elimination aims to eradicate HCV by addressing special population groups that have a known higher HCV prevalence rather than merely screening the entire population; hemodialysis-dependent patients are one of the population groups targeted [6]. Despite the excellent efficacy of AVT, the current goal is hardly attainable.

CHC is far more prevalent in hemodialysis (HD)-dependent patients as they undergo frequent invasive medical procedures and are prone to nosocomial spread; consequently, the risk increases with time spent on dialysis [6]. The most recent report on the dialysis status in Poland demonstrated that the number of hemodialyzed patients exceeded 18,000 with a 3.8% HCV seroprevalence: 10-fold more than in the general population [7].

CHC is a well-recognized risk factor for increased liver-related morbidity and mortality in patients on renal replacement therapy (RRT), and successful HCV elimination improves clinical outcomes. Additionally, CHC in HD-dependent patients negatively affects overall survival and results in an increased risk of cirrhosis, HCC, and a lower quality of life compared to their HCV-negative counterparts [6,8,9]. Therefore, all patients with end-stage renal disease (ESRD) should be considered for AVT [1,10,11].

Former interferon-based therapies were neither effective nor well-tolerated, which deterred from AVT commencement [6]. With the advent of oral direct-acting antiviral agents (DAAs), which are highly effective and well-tolerated, the landscape has dramatically changed. Currently, a few treatment options are available for patients with CHC on RRT, including a fixed-dose combination of glecaprevir and pibrentasvir, sofosbuvir and velpatasvir or grazoprevir and elbasvir, not requiring dose adjustments [1,10]. The latter option has applications only for genotype 1b of HCV. In cases of decompensated cirrhosis and severe renal impairment, a fixed-dose combination of sofosbuvir and velpatasvir, without ribavirin, for 24 weeks is recommended. Despite the advent of DAAs, patients on hemodialysis have been reportedly left untreated for reasons not yet elucidated [8].

As aforementioned, eradication of HCV requires a comprehensive strategy to succeed; therefore, efforts are made not only for HCV treatment but also for the prevention of HCV transmission. Despite the implementation of multiple precautions, HCV spread within dialysis centers continues, with the prevalence of HCV as a contributing factor [11–14]. The prevalence of HCV may be reduced with DAAs; however, the risk of reinfection persists if the patient remains on maintenance hemodialysis. However, little is known about the management practices of patients on hemodialysis, from a nephrological standpoint, after they achieve sustained virologic response (SVR) and whether these practices prevent HCV reinfection.

Disease progression of CHC results in liver inflammation and fibrosis, which may be mitigated to a certain extent by DAAs [15]. It should be highlighted that HCV eradication constitutes only the first step because not all subjects who eradicated the virus are entirely cured; long-accumulated histopathological changes may persist. Therefore, continued surveillance of cured patients is mandatory to prevent undermining efforts put forth for HCV eradication. This can be achieved through the evaluation of fibrosis. It has been documented that liver fibrosis can be utilized for the prognostication of adverse outcomes, patient mortality and as a predictor of decompensation or hepatocellular carcinoma (HCC) occurrence [16,17]. It has also been reflected in the most recent Kidney Disease: Improving Global Outcomes (KDIGO) Work Group guidelines which recommend that all patients with chronic kidney disease (CKD) and CHC be evaluated for fibrosis using noninvasive biomarkers, such as fibrosis-4 (FIB-4), aspartate transaminase-to-platelet ratio index (APRI), or transient elastography [11].

CHC is a major cause of the occurrence of HCC [18]. Patients with CHC and those that achieved SVR but have advanced fibrosis or cirrhosis should undergo regular screening for HCC with ultrasound and alpha-fetoprotein (AFP) assay [1,10]. Knowledge of the fibrosis stage enables better HCC stratification and optimization of HCC surveillance.

The insufficient donor supply available for transplantation, the growing needs in this matter, and access to effective AVT have encouraged transplant centers to broaden donor pools by utilizing HCV viremic donors. There is no agreement across transplant centers on whether this direction is right; however, it has been supported by the KDIGO guidelines [11]. Considering HCV elimination efforts, this additional pool of patients will become limited with time; hence, it is crucial to use this time wisely for the benefit of HD-dependent patients.

The aim of this study was to investigate the HCV management practices across dialysis centers in Poland and identify potential barriers that prevent us from reaching the goal of HCV elimination by 2030. We strongly believe that identifying obstacles could be the first step toward HCV elimination in the ESRD population in the authors' country.

2. Materials and Methods

2.1. Study Administration

The study was conducted between January and December 2022. Both private and public adult hemodialysis (HD) centers in Poland, which were active in 2022 (n = 260), were approached for the survey via email, and only one representative (medical doctor) of each unit was to complete the survey. Each HD center was represented only once. Questionnaires were administered to the head of the HD unit. Only they had the authority to complete the form unless it was specifically requested by the HD center to assign another email address to them. In this case, the access of the previous email address owner to the questionnaire was revoked. The survey was performed anonymously, and the questionnaire was blocked once the form was received from the respective addressee to prevent double submissions. The HD centers were notified of the survey thrice. The questionnaire consisted of 14 multi-choice, semi-open questions.

The study was conducted in line with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Warsaw (AKBE/205/2021).

2.2. Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 25. A series of frequency analyses and χ^2 or exact Fisher Tests were performed. p values of < 0.05 were considered significant. An χ^2 or exact Fisher test was used to study differences between public and private facilities and between tertiary and secondary units. The effect size was measured with the V Cramer coefficient.

The results are presented as percentages and frequencies or means and standard deviations, whichever was appropriate. Percentages were calculated using the overall number of valid responses to each question as the denominator. If the respondent left the question blank, it was excluded from the denominator. For multiple-choice questions, the number of participants responding to that particular question constituted the total number in the denominator. Consequently, for these questions, the column totals exceeded 100%.

3. Results

A total of 112 HD centers responded, representing 43.1% of all HD centers in Poland. The majority of them were private (n = 79, 70.5%), with an overall 8080 (28–176 pts) patients being managed within the surveyed facilities; this patient count accounts for 43.4% of the patient volume that is on maintenance hemodialysis in Poland. Out of 33 public facilities, 11.6% constituted tertiary units. The surveyed professionals were mainly heads of the HD centers and board-certified nephrologists (Table 1).

Table 1. Participants characteristics.

Variable		N = 112
Type of the facility		
Private	N (%)	79 (70.5)
Public	N (%)	33 (29.5)
Tertiary hospital	N (%)	13 (11.6)
Secondary hospital	N (%)	20 (17.9)
Role of the respondent within each HD center		
Head of department	N (%)	91 (81.2)
Dialysis physician	N (%)	21 (18.8)

Table 1. *Cont.*

Variable			N = 112
Number of HD patients		Mean, (SD)	72.1 (32.6)
Number of anti-HCV + patients		Mean, (SD)	2.8 (2.3)
Number of patients with active viremia		Mean, (SD)	0.9 (1.43)
Specialty of the respondent			
	Nephrology	N (%)	107 (95.5)
	Internal medicine	N (%)	100 (89.3)
	Transplant medicine	N (%)	13 (11.6)
	Pulmonary disease	N (%)	4 (3.6)
	Family medicine	N (%)	2 (1.8)
	Diabetology	N (%)	2 (1.8)
	Geriatrics	N (%)	1 (0.9)

HD; hemodialysis center.

3.1. Detailed Survey Questions

3.1.1. Do You Refer Patients with CHC for AVT as a Routine Practice?

Five responders, all from public facilities, did not provide an answer to the question. Of the remaining facilities, 91.6% (n = 98) claimed to refer HD patients for AVT as a routine practice, whereas 8.4% (n = 9) reported otherwise (Table 2).

Table 2. Attitudes, strategies, and obstacles in HCV care among dialysis centers in Poland.

Survey Question			Response, *n* (%)
Do you consider patients with CHC for AVT as a routine practice?			
	Yes	N (%)	98 (91.6)
	No	N (%)	9 (8.4)
Where are subjects typically referred for AVT?			
	Infectious disease physician	N (%)	94 (83.9)
	Hepatologists	N (%)	19 (17.0)
	Transplant center	N (%)	2 (1.8)
Why are hemodialysis patients with CHC not referred for AVT?			
	All patients are referred for AVT	N (%)	28 (27.7)
	Patients are unwilling to undergo AVT	N (%)	41 (40.6)
	Contraindication to AVT	N (%)	19 (18.8)
	Short life expectancy	N (%)	11 (10.9)
	Lack of awareness of AVT	N (%)	9 (8.9)
	Fear of AVT-induced AEs	N (%)	7 (6.9)
	Organizational matters	N (%)	6 (5.9)
	Unavailability of DAAs	N (%)	6 (5.9)
	Decision of the outpatient unit	N (%)	3 (3.0)
	Fear of drug-drug interactions	N (%)	3 (3.0)
	Low efficacy of AVT	N (%)	2 (2.0)
Do you evaluate patients with CHC for liver fibrosis within the HD center?			
	No	N (%)	61 (60.4)
	Yes	N (%)	40 (39.6)
	Subject referred to AVT only	N (%)	30 (29.7)
	Subject with elevated ALT only	N (%)	1 (0.9)
Do you screen patients with CHC for HCC within the HD center?			
	No	N (%)	54 (53.5)
	Yes	N (%)	47 (46.5)

Table 2. *Cont.*

Survey Question		Response, *n* (%)
What is your HCC surveillance model for patients with CHC?		
USG every 6 months	N (%)	24 (21.4)
AFP every 6 months	N (%)	13 (11.6)
USG every 12 months	N (%)	12 (10.7)
AFP every 12 months	N (%)	2 (1.8)
In HBV/HCV co-infection only	N (%)	6 (5.4)
In cirrhotic patients only	N (%)	5 (4.5)
If specifically recommended by the infectious disease outpatient clinic only	N (%)	2 (1.8)
Would you offer an HCV viremic kidney to aviremic recipient?		
Yes	N (%)	54 (48.2)
No	N (%)	54 (48.2)
Decision of the recipient	N (%)	3 (2.7)
Would require consulting	N (%)	1 (0.9)
Where are dialyzed patients following successful HCV eradication?		
Along with HCV-naïve patients	N (%)	49 (46.7)
On machines dedicated to hepatitis patients	N (%)	43 (40.9)
Dedicated machine following SVR	N (%)	13 (12.4)

CHC, chronic hepatitis C; HCV, hepatitis C virus; HBV, hepatitis B virus; AVT, antiviral treatment; DAAs, direct oral antiviral agents; HD, hemodialysis; USG, ultrasonography; AFP, alpha-fetoprotein; AEs, adverse events; SVR, sustained virologic response; ALT, alanine transaminase; HCC, hepatocellular carcinoma.

3.1.2. Where Are Subjects Typically Referred to for AVT?

The vast majority of respondents (83.9%, *n* = 94) refer CHC individuals to infectious disease outpatient clinics to be evaluated for AVT, followed by hepatology outpatient clinics (17%, *n* = 19) (Table 2).

3.1.3. Why Are Hemodialysis Patients with CHC Not Considered for AVT?

Eleven HD centers did not answer the question and declared not to have had CHC patients recently and were not able to answer the question based on their current population experience. Within the remaining number of HD centers, twenty-eight units (27.7%) declared to consider all subjects for AVT. The primary reason for not referring patients on RRT for AVT was patients' unwillingness to undergo CHC treatment (*n*= 41, 40.6%), followed by contraindications to AVT (*n* = 19, 18.8%) and short life expectancy (*n* = 11, 10.9%). Lack of knowledge of CHC management and potential AVT-induced adverse reactions was reported as a deterrent factor to AVT in 8.9% (*n* = 9) and 6.9% (*n* = 7) of cases, respectively. Organizational matters, the most reported being the distance to the outpatient clinic and lack of availability of DAAs, were each reported in 5.9% (*n* = 6) of cases (Table 2).

3.1.4. Do You Evaluate Patients with CHC for Liver Fibrosis within the HD Center?

Lack of routine liver fibrosis assessment in patients with CHC prevailed (60.4%). Forty dialysis units declared to assess liver fibrosis; however, this was limited to 75% in subjects referred for AVT only.

3.1.5. Do You Screen Patients with CHC for HCC within the HD Center? What Is Your HCC Surveillance Model for Patients with CHC?

HCC surveillance was exercised in as many as 47 dialysis centers (46.5%), while 54 (53.5%) confirmed not having HCC surveillance for patients with CHC. The predominant HCC surveillance model was an ultrasound examination every six months followed by AFP with the same frequency (Table 2).

3.1.6. Where Are Dialyzed Patients following Successful HCV Eradication?

Seven HD centers did not provide an answer to the question. Virtually half of the respondents (46.7%, *n* = 49) dialyzed their patients—after they achieved SVR—along with

HCV-naïve individuals, whereas the second most common practice (40.9%, n = 43) was the utilization of dedicated machines for HCV-viremic patients (Table 2).

3.1.7. Would You Offer an HCV Viremic Kidney to an Aviremic Recipient?

Fifty-four responders (48.2%) declared to consider offering HCV-viremic kidney allografts to HCV-aviremic kidney transplant candidates, and the remaining centers did not consider such an option. Fear of potential complications following kidney transplantation (KTx) from an HCV-viremic donor to an HCV-negative recipient (HCV NAT D+/R− was a prominent deterrent factor (n = 39, 72,2%), followed by lack of confidence in the efficacy of DAAs after kidney transplant (n = 27, 50%) (Table 2).

3.2. Differences in HCV Management Practices between Private and Public HD Centers

There were no significant differences between private and public dialysis centers in terms of patients with CHC being referred for AVT (n = 92.2% vs. 90.0%, respectively; p = 0.708). Similarly, no differences were found in reasons for not referring patients with CHC for AVT; however, compared to private centers, a lack of knowledge on AVT was more often reported from public centers, with the effect size being small (3.8% vs. 18.2%, respectively, p = 019, V = 0.24) (Table 3).

Table 3. Differences in HCV care between private and public hemodialysis centers in Poland.

Survey Question			Response, n (%) Private	Response, n (%) Public	
Do you consider patients with CHC for AVT as a routine practice?					
Yes		N (%)	71 (92.2)	27 (90.0)	p = 0.708
No		N (%)	6 (7.8)	3 (10.0)	
Why are hemodialysis patients with CHC not referred for AVT?					
All patients are referred for AVT		N (%)	23 (29.1)	5 (15.2)	$\chi^2(1)$ = 2.42 p = 0.120
Patients are unwilling to undergo AVT		N (%)	29 (36.7)	12 (6.4)	$\chi^2(1)$ = 0 p = 0.972
Contraindication to AVT		N (%)	12 (15.2)	7 (21.2)	$\chi^2(1)$ = 0.60 p = 0.439
Short life expectancy		N (%)	8 (10.1)	3 (9.1)	p = 1
Lack of awareness of AVT		N (%)	3 (3.80	6 (18.2)	p = 0.019 V = 0.24
Fear of AVT-induced AEs		N (%)	5 (6.3)	2 (6.1)	p = 1
Organizational matters		N (%)	4 (5.1)	2 (6.1)	p = 1
Unavailability of DAAs		N (%)	4 (5.1)	2 (6.1)	p = 1
Decision of the outpatient unit		N (%)	1 (1.3)	2 (6.1)	p = 0.207
Fear of drug-drug interactions		N (%)	2 (2.5)	1 (3.0)	p = 1
Low efficacy of AVT		N (%)	2 (2.5)	0 (0.0)	p = 1
Do you evaluate patients with CHC for liver fibrosis within the HD center?					
No		N (%)	44 (62.0)	17 (56.7)	$\chi^2(1)$ = 0.20 p = 0.656
Yes		N (%)	27 (38.0)	13 (43.3)	
Only referred for antiviral treatment		N (%)	23 (32.4)	7 (23.3)	
Only patients with abnormal aminotransferases		N (%)	0 (0.0)	1 (3.3)	
Do you screen patients with CHC for HCC within the HD center?					
Yes		N (%)	30 (42.9)	17 (54.8)	$\chi^2(1)$ = 1.24 p = 0.266
No		N (%)	40 (57.1)	14 (45.2)	

Table 3. *Cont.*

Survey Question		Response, *n* (%) Private	Public	
What is your HCC surveillance model for patients with CHC?				
Ultrasound every 12 months	N (%)	8 (10.1)	4 (12.1)	$p = 0.746$
Ultrasound every 6 months	N (%)	13 (16.5)	11 (33.3)	$\chi^2(1) = 3.94$ $p = 0.047$ $V = 0.19$
AFP every 12 months	N (%)	1 (1.3)	1 (3.0)	$p = 0.504$
AFP every 6 months	N (%)	5 (6.3)	8 (24.2)	$p = 0.019$ $V = 0.26$
Patients with HBV co-infection only	N (%)	6 (7.6)	0 (0.0)	$p = 0.177$
Patients with cirrhosis only	N (%)	3 (3.8)	2 (6.1)	$p = 0.630$
If specifically recommended by the infectious disease outpatient clinic only	N (%)	1 (1.3)	1 (3.0)	$p = 0.504$
Where are dialyzed patients following successful HCV eradication?				
Along with HCV naïve patients	N (%)	31 (42.5)	18 (56.2)	χ^2 (2) = 1.96 $p = 0.352$
On machines dedicated to hepatitis patients	N (%)	33 (45.2)	10 (31.3)	
Dedicated machine following SVR	N (%)	9 (12.3)	4 (12.5)	

CHC, chronic hepatitis C; AVT, antiviral treatment; DAAs, direct oral antiviral agents; HD, hemodialysis; USG, ultrasonography; AFP, alpha-fetoprotein; HCV, hepatitis C virus; AEs, adverse events; HCC, hepatocellular carcinoma.

Routine liver fibrosis or HCC surveillance practices did not vary between the public and private dialysis centers ($p = 0.656$, $\chi^2(1) = 0{,}20$; $p = 0.266$, $\chi^2(1) = 1{,}24$, respectively). However, when detailed HCC surveillance protocols were analyzed, public centers declared that they performed USG examination and AFP every 6 months, which was significantly more often compared to private centers (USG, 33.3% vs. 16.5%, $\chi^2(1) = 3.94$, $p = 0.047$, $V = 0.19$; AFP, 24.2% vs. 6.3%, $p = 0.019$, V = 0.26, respectively) (Table 3).

When asked about the dialysis machine used for the management of patients with CHC after they achieved SVR, no significant differences were reported ($\chi^2(2) = 1.96$; $p = 0.352$) (Table 3).

3.3. Differences between Hemodialysis Centers within Tertiary and Secondary Hospitals in Poland

No statistical difference was noted in terms of HD centers referring patients with CHC for AVT within the tertiary and secondary hospitals ($p = 0.279$) (Table 4). Similar reasons were also found for not considering the patients on RRT for AVT (Table 4).

Table 4. Differences in HCV care between tertiary and secondary hemodialysis centers in Poland.

Survey Question		Response, *n* (%) Tertiary	Secondary	
Do you consider patients with CHC for AVT as a routine practice?				
Yes	N (%)	11 (100.0)	16 (84.2)	$p = 0.279$
No	N (%)	0 (0.0)	3 (15.8)	
Why are hemodialysis patients with CHC not referred for AVT?				
All patients are referred for AVT	N (%)	3 (23.1)	2 (10.0)	$p = 0.360$
Patients are unwilling to undergo AVT	N (%)	4 (30.8)	8 (40.0)	$p = 0.719$
Contraindication to AVT	N (%)	2 (15.4)	5 (25.0)	$p = 0.676$
Short life expectancy	N (%)	1 (7.7)	2 (10.0)	$p = 1$
Lack of awareness of AVT	N (%)	2 (15.4)	4 (20.0)	$p = 1$
Fear of AVT-induced AEs	N (%)	0 (0.0)	2 (10.0)	$p = 1$
Organizational matters	N (%)	0 (0.0)	2 (10.0)	$p = 0.508$
DAAs unavailability	N (%)	0 (0.0)	2 (10.0)	$p = 0.508$
Decision of the outpatient unit	N (%)	1 (7.7)	1 (5.0)	$p = 1$
Fear of drug-drug interactions	N (%)	0 (0.0)	1 (5.0)	$p = 1$
Low efficacy of AVT	N (%)	0 (0.0)	0 (0.0)	-

Table 4. *Cont.*

Survey Question		Response, *n* (%) Tertiary	Secondary	
Do you evaluate patients with CHC for liver fibrosis within the HD center?				
No	N (%)	1 (9.1)	16 (84.2)	$p < 0.001$
Yes	N (%)	10 (90.9)	3 (15.8)	$V = 0.74$
Only referred for antiviral treatment	N (%)	5 (45.5)	2 (10.5)	
Only patients with abnormal aminotransferases	N (%)	1 (9.1)	0 (0.0)	
Do you screen patients with CHC for HCC within the HD center?				
Yes	N (%)	7 (63.6)	10 (50.0)	$\chi^2(1) = 1.11$
No	N (%)	4 (36.4)	10 (50.0)	$p = 0.293$
What is your HCC surveillance model for patients with CHC?				
Ultrasound every 12 months	N (%)	4 (30.8)	0 (0.0)	$p = 0.017$ $V = 0.46$
Ultrasound every 6 months	N (%)	4 (30.8)	7 (35.0)	$p = 1$
AFP every 12 months	N (%)	1 (7.7)	0 (0.0)	$p = 0.394$
AFP every 6 months	N (%)	5 (38.5)	3 (15.0)	$p = 0.213$
Patients with HBV co-infection only	N (%)	0 (0.0)	0 (0.0)	-
Patients with cirrhosis only	N (%)	0 (0.0)	2 (10.0)	$p = 0.508$
If specifically recommended by the infectious disease outpatient clinic only	N (%)	1 (7.7)	0 (0.0)	$p = 0.394$
Where are dialyzed patients following successful HCV eradication?				
Along with HCV naïve patients	N (%)	6 (50.0)	12 (66.6)	
On machines dedicated to hepatitis patients	N (%)	4 (33.3)	6 (33.3)	$p = 0.882$
Dedicated machine following SVR	N (%)	2 (16.7)	2 (11.1)	

CHC, chronic hepatitis C; AVT, antiviral treatment; DAAs, direct oral antiviral agents; HD, hemodialysis; AFP, alpha-fetoprotein; HCV, hepatitis C virus; AEs, adverse events; HCC, hepatocellular carcinoma.

Significantly more tertiary institutions assessed liver fibrosis in patients with CHC than their secondary counterparts ($p < 0.001$, V = 0.74). Attitude towards the HCC survival protocol was similar in the tertiary and secondary hospitals ($\chi^2(1) = 1{,}11$, $p = 0.293$), and so was the machine used for subjects who eradicated the virus $p = 0.882$ (Table 4).

4. Discussion

This national survey is the first to analyze HCV attitudes and care practices in Poland. This study identified noteworthy differences in HCV management strategies across HD centers in Poland, along with the vulnerability of the national HCV infrastructure in terms of the ESRD population.

Surveyed HD centers reported to have 316 anti-HCV positive patients, including 101 with active viremia, which constitutes 3.9% and 1.25%, respectively, of the total hemodialysis population volume in Poland. This is congruent with the most recent national report on hemodialysis status in Poland, in which the estimated prevalence of anti-HCV prevalence was 3.8% and active viremia 1.1%. This may underscore the fact that the sample was representative [7].

A vast majority of surveyed HD centers declared that they routinely refer patients for AVT, and only less than 10% did not. Nevertheless, of the HD centers referring patients for AVT, 46% pointed to obstacles hindering patients from actually being treated. The primary reason for the lack of AVT commencement was patients' reluctance to undergo therapy, followed by organizational barriers and/or lack of DAAs availability. In such a scenario, an impressive percentage of HD centers that consider patients for AVT may seem to be overly optimistic and may not yield desirable effects in the form of HCV elimination. Currently recommended AVT schedules with reduced pills burden and short treatment duration are quite convenient from the patient's perspective; therefore, we may speculate that the subject's averseness, at least to some extent, stems from a lack of expertise among dialysis physicians or being hesitant towards AVT themselves which was documented in more than 20% of our responders and may result from previous interferon

experience. This issue has been likewise raised in other papers [19,20]. Importantly, it has been previously documented that patients on maintenance hemodialysis mostly rely on their dialysis physician's opinion on medical-related matters. A more granular analysis of patient reluctance is required to fully elucidate the root cause and address it with relevant corrective measures.

Surprisingly many responders pointed to contraindications to AVT as a reason for not treating the patient compared to drug-drug interactions. With the current AVT armamentarium, contraindications are very limited and mostly related to interactions with concomitant medication, e.g., anticonvulsants. We may presume that those results may similarly stem from little expertise on the current CHC treatment landscape. Owing to the anonymous nature of the survey, we were not able to verify with responders which contraindication they were referring to specifically.

Our survey indicates that most HD centers refer their patients to infectious disease outpatient clinics to be evaluated for AVT. Given the specificity of the ESRD population, distance to the outpatient clinic and long waiting time for the appointment may be a deterrent factor and bottleneck for HCV elimination, especially since the time to the first visit in an infectious disease clinic may exceed 9 months in some regions. Polish HD centers do not have direct access to DAAs; therefore, the only solution is to await specialist consultation, resulting in linkage to care being often unsuccessful.

Now that the general recommendation for AVT may be applied to HD-dependent subjects, the population should be an easy target for HCV eradication. Nonetheless, the current HCV care model needs to be simplified to ensure optimal coordination of treatment and to reduce waiting time. During their most recent congress, the WHO also urged towards a similar direction, pointing to decentralization and radical simplification of hepatitis care [21].

We strongly believe that linkage to care could be improved by engaging dialysis physicians in the DAA-prescribing process. Now that highly effective AVT with impressive tolerability is available, the trend towards decentralization and task-sharing approach in HCV management is justifiable, especially since HCV management may be successful regardless of the level of expertise of the treating physician [22]. Moreover, nephrologists taking the initiation may streamline care and reduce the number of visits outside the dialysis unit and referrals to specialists, shorten the time to AVT initiation, and ensure close monitoring of the treatment within the HD center.

Undoubtedly, not all AVT could be coordinated within the HD unit; however, there is a pool of patients, such as treatment-naïve patients or those without decompensated cirrhosis, who could be successfully treated within HD centers with great success. The most demanding patients, i.e., DAA non-responders or those with decompensated cirrhosis, could be referred to an infectious disease specialist/hepatologist. Detailed suggestions on possible solutions to HCV management practices improvement have been summarized in Table 5.

Many tools and solutions facilitate HCV management in hepatitis non-expert settings. First, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) came forward with a simplified treatment guidance for HCV-naïve individuals and those with compensated cirrhosis, which with remote support from a hepatitis specialist was proved to be successful [10,23]. Such remote consultations could be arranged between hepatitis experts and dialysis physicians, which could be more efficient than the referral system. Furthermore, the use of pangenotypic agents does not mandate regiment adjustment per genotype, and no dose adjustment is needed in the ESRD population if the European Association for the Study of the Liver (EAS)L or AALSD/IDSA guidelines are followed [1,10]. Drug-drug interactions between DAAs and other medications may be successfully verified using the University of Liverpool online tool (hep-druginterations.org/checker). Liver stiffness may be assessed with routine blood tests, Fib-4, and APRI if transient elastography is not available [1,10].

Table 5. Solutions on local and national levels to improve HCV management in hemodialysis centers in Poland.

Local Level	National Level
Refrain from isolating HCV-positive subjects and those who achieved SVR in the hemodialysis setting Comprehensive hepatitis training among dialysis physicians with the main focus being put on the following: - current treatment options and simplified approach towards AVT, - benefits of AVT, - contraindication for AVT, - tools for fibrosis evaluation and predictive cut-off values, - need for HCC surveillance following SVR in subjects with advanced fibrosis/cirrhosis Training on infectious control strategies among dialysis staff with regular audits to assure compliance. Regular screening for possible HCV reinfection and/or outbreaks within HD centers The root cause of patients' reluctance to AVT needs to be further investigated and addressed with respective measures depending on the outcome, e.g., educating patients by the trained dialysis nurse.	Dialysis physicians taking over the AVT in patients on HD and with CHC. DAAs to be available in HD centers for CHC management. National consultants could be engaged to issue a recommendation on obligatory fibrosis evaluation in all patients on hemodialysis and with CHC, followed by HCC surveillance. Possibility of consulting with hepatitis expert needs to be assured (remotely, if possible). Amount of paperwork needs to be reduced in order to facilitate DAAs administration in HD centers.

CHC, chronic hepatitis C; AVT, antiviral treatment; DAAs, direct oral antiviral agents; HD, hemodialysis; AFP, alpha-fetoprotein; HCV, hepatitis C virus; HCC, hepatocellular carcinoma, SVR; sustained virologic response.

Nonetheless, delegating AVT to HD centers requires a suitable infrastructure, including funds and training allocation. The amount of paperwork and time constraints may hamper nephrologists' involvement.

More than half (60%) of the HD centers claimed that they did not assess liver fibrosis routinely in patients with CHC, while in another 30%, fibrosis was assessed only in patients prescribed AVT. Given the above and the multitude of barriers reported in our survey preventing HD-dependent patients from receiving AVT, many individuals may be left untreated without accurate liver fibrosis assessment, despite continued HCV-related abnormalities accumulation. Importantly, fibrosis may serve as a predictor of decompensation or of HCC in patients with CHC, which is why it is important to monitor liver stiffness as recommended by KDIGO [11,16,17].

Liver fibrosis assessments may be even more critical for HD-dependent patients waitlisted for a kidney transplant. It has been previously demonstrated that HD-dependent patients may have liver injury without aminotransferase elevation, as they do not reflect the liver injury decisively in this population. Advanced fibrosis does not exclude patients from receiving kidney transplants; however, it may pose a risk of portal hypertension-related complications. Therefore, fibrosis assessment in patients with known liver injury would facilitate the discussion and decision-making process in terms of AVT, particularly in patients who decline the opportunity for treatment. Another subset of patients who could benefit from liver fibrosis assessment would be kidney transplant candidates, if diagnosed with cirrhosis with indirect fibrosis indices prior to transplantation, who could qualify for both a liver-kidney transplant rather than a kidney transplant alone. Given the progressive nature of liver fibrosis in HCV-infected individuals, some authors have pointed out the need for repeated liver fibrosis assessments in HD-dependent patients waitlisted for KTx, with the assessments conducted at a frequency based on the initial score.

Moreover, responders pointed to a lack of equipment for liver fibrosis assessment, whereas recommendations clearly state that, prior to AVT, liver fibrosis assessment may be based on both transient elastography and routine biochemical results without any dedicated equipment [1,10]. Therefore, we may speculate that the lack of liver fibrosis assessment implies a lack of awareness of available tools and the importance of fibrosis assessments among dialysis physicians.

Furthermore, the majority of responders declared that their facilities do not routinely impose HCC surveillance protocols in patients with CHC, including six HD units that screen patients for HCC only when HBV/HCV coexist and another five that only screen patients with cirrhosis; two replied that they screen purely on infectious disease outpatient clinic recommendations without having an internal HCC surveillance protocol. Others pointed out that currently, they only have HCV-cured patients under their care, which may indicate that, in their view, this population does not require oncological surveillance.

Importantly, the EASL and AASLD recommend HCC screening in the CHC untreated population; however, all subjects following SVR with advanced fibrosis at baseline (F3,F4) should also be screened for HCC with ultrasound examination bi-annually with or without AFP [1,10].

Given the reluctance to undergo AVT, a substantial number of patients may be subjected to prolonged active viremia, resulting in continued liver damage. HCC diagnosis may be made at more advanced stages with a poor prognosis and limited treatment options when the abovementioned factors are coupled with a lack of mandatory fibrosis evaluation.

The WHO 's goal of reducing HCV-related morbidity and mortality cannot be ascertained without proper fibrosis and HCC surveillance. There is a need to improve nephrologist awareness of HCV care standards to allow for knowledgeable patient management in this area.

Virtually half of the responders declared that they managed patients with CHC following SVR on machines that were dedicated for patients with hepatitis, while some placed them separately on dedicated machines for patients that achieved SVR. Interferon-based therapies with a high risk of viral relapse, as seen previously, justified such practices. However, with the availability of DAA, the approach does not stand to reason. Furthermore, isolation of HCV viremic patients has not been firmly confirmed as an effective measure to prevent HCV spread, but in certain circumstances, for example, low patient:personnel ratio, it may be justified [9,24,25]. Epidemiological investigations have shown that patients dialyzed nearby are at a greater risk of HCV infection than those dialyzed on the same machine as HCV viremic ones [9,14]. This may imply that non-adherence to mandatory precautions and not the machine itself is an obstacle to eradicating CHC; this factor requires due consideration rather than mere isolation of patients with CHC.

It should be noted that patients who achieve SVR with interferon-free regimens are free from the virus, with viral relapse being highly unlikely, which is reflected in CDC guidelines that recommend the management of such patients along with HCV-naïve counterparts [12]. The KDIGO advocates against the isolation of HCV-infected patients in HD settings [11]. Importantly, isolating HD-dependent patients that achieved SVR from HCV viremic individuals may be even more harmful. This not only creates an impression that they have not been cured of the virus and deters other viremic patients from AVT but also puts them at greater risk of reinfection, especially in case of faulty infection control precautions and regular HCV RNA testing not being a part of routine practice. Managing patients who eradicated the virus on dedicated machines is unjustifiable and may produce unnecessary organizational burdens.

Patients who have been successfully cured of the virus should be dialyzed along with HCV-naïve patients with universal precautions measures being respected, and this is most effective in preventing within-unit HCV spread, whereas separating patients with HCV is illegitimate.

Currently, the utilization of HCV viremic organs is increasing [26]. This is mainly driven by the opioid epidemic, a shrinking donor pool, and a long waitlist time. The present study shows that virtually half of the responders were comfortable with offering HCV viremic organs to potential organ recipients; however, the majority allowed such an option only in HCV viremic recipients. We agree that HCV viremic organs should be considered for HCV viremic recipients as the first preference; however, naïve recipients should not be deprived of this choice, especially in centers with long waitlist times or highly immunized kidney transplant candidates. This approach is congruent with KDIGO's most

recent guidelines, highlighting that all kidney transplant candidates should be considered for an HCV-infected allograft, regardless of their HCV status [11].

In the authors' country, this scenario is currently unlikely because donors are not routinely verified for viremia with HCV RNA NAT assay prior to transplantation, and only patients with CHC can be offered anti-HCV + organs, thereby preventing the determination of the actual risk of transmission and informative decision-making. We may speculate that up to 40% of anti-HCV + donors could be aviremic and could donate an organ to aviremic recipients with a marginal risk of viral transmission, given the spontaneous HCV eradication rate.

Among opponents of HCV NAT D+/R- transplants, three-thirds substantiated their attitude by citing a great risk of potential complications following KTx, followed by a lack of confidence in terms of AVT efficacy in the post-kidney transplant setting. Receiving organs from aviremic donors is always preferred. However, owing to the shrinking donor pool, kidney transplant candidates may not survive until being offered one. The Polish national organization for organ transplantation (Poltransplant) report revealed that in 2021, 126 waitlisted kidney transplant candidates died without receiving a transplant; the average waitlist time for the first kidney transplant was 442 days, while highly immunized patients remained waitlisted for up to 1452 days [27]. Contrarily, there is a body of evidence to suggest that HCV NAT D+/R- transplant may not only be a favorable solution compared to remaining on HD, but it also does not necessarily entail additional complications. Importantly, HCV NAT D+/R- transplant should always be preceded by a properly informed consent process, and AVT should be administered without delay [26].

It can be further argued that the dialysis physician is not in charge of KTx matters; however, it has been proved that HD-dependent patients rely highly on their community nephrologists' options [28]. Therefore, it is our obligation as physicians to provide patients with up-to-date and evidence-based information, enabling them to make informed decisions.

Despite the fact that Poltransplant records indicate that there was only one patient who was rejected as a donor owing to HCV-positive status, we may presume that this number may be underestimated; such potential donors may never be reported knowing the HCV serostatus [27].

Given the WHO HCV eradication target, HCV viremic donors are a finite and temporary source of additional organs. It should be used wisely for the benefit of kidney transplant candidates.

Limitations

This study has some limitations. First, not all HD units were represented. However, the 43% response rate is similar to other surveys among HD centers, and the responding centers represent 43% of the adult HD-dependent population volume. Moreover, the consistency of the presented findings when compared to the national report data supports the idea that the study sample is representative. Our findings demonstrated practices and attitudes as they were reported, and the accuracy of actual practices and attitudes at the center could not be verified.

5. Conclusions

In conclusion, the present study demonstrated great disparities in HCV management practices and monitoring after virus elimination across HD centers in Poland. Differences in attitudes and HCV-care protocols may hinder the goal of HCV eradication by 2030. However, HCV eradication is no longer merely a pipe dream, and it may certainly become a reality. Nevertheless, there is a need to optimize and streamline HCV management infrastructure in patients with ESRD. A great emphasis needs to be put on a comprehensive training program dedicated to dialysis physicians to improve their poor performance in terms of fibrosis/cirrhosis evaluation and HCC surveillance in CHC patients.

Author Contributions: Conceptualization, P.C.; methodology, P.C. and K.C.; validation, P.C. and O.T.; formal analysis, P.C. and K.C.; investigation, W.Z.-W.; data curation, K.C.; writing—original draft preparation, P.C.; writing—review and editing, O.T. and M.D.; visualization, K.C.; supervision, T.B.; project administration, P.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Warsaw (AKBE/205/2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: Data supporting the results reported in the article can be found under the following https://doi.org/10.17632/ch8rh343m9.1.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. *J. Hepatol.* **2020**, *73*, 1170–1218. [CrossRef] [PubMed]
2. Zakrzewska, K.; Stepien, M.; Rosinska, M. Wirusowe zapalenie wątroby typu C (WZW typu C) w Polsce w 2018 roku. *Przedl Epidemiol.* **2020**, *74*, 209–2022. (In Polish) [CrossRef] [PubMed]
3. Polaris Observatory HCV Collaborators. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: A modeling study The Polaris Observatory HCV Collborators. *Lancet Gastroenterol. Hepatol.* **2022**, *7*, 396–415. [CrossRef]
4. Blach, S.; Zeuzem, S.; Manns, M.; Altraif, I.; Duberg, A.-S.; Muljono, D.H. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *Lancet Gastroenterol. Hepatol.* **2017**, *2*, 161–176. [CrossRef]
5. World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016–2021. *Towards Ending Viral Hepatitis*; World Health Organization, 2016. Available online: https://apps.who.int/iris/handle/10665/246177 (accessed on 2 February 2023).
6. Fabrizi, F.; Martin, P.; Dixit, V.; Messa, P. Hepatitis C virus infection and kidney disease: A meta-analysis. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 549–557. [CrossRef] [PubMed]
7. Debska-Slizien, A.; Rutkowski, B.; Jagodzinski, P.; Przygoda, J.; Lewandowska, D.; Czerwinski, J.; Kamiński, A.; Gellert, R. Aktualny stan leczenia nerkozatepczego w Polsce—2021. *Nefrol. Dial. Pol.* **2021**, *25*, 85–103. (In Polish)
8. Goodkin, D.A.; Bieber, B. Hemodialysis Patients with Hepatitis C Infection Are Not Receiving the New Antiviral Medications. *Am. J. Nephrol.* **2015**, *41*, 302. [CrossRef]
9. Fabrizi, F.; Cerutti, R.; Messa, P. Updated Evidence on the Epidemiology of Hepatitis C Virus in Hemodialysis. *Pathogens* **2021**, *10*, 1149. [CrossRef]
10. AASLD/IDSA HCV Guidance Panel. Recommendations For Testing. *Managing and Treating Hepatitic C.* Available online: http://www.hcvguidelines.org/ (accessed on 22 February 2023).
11. Jadoul, M.; Awan, A.A.; Berenguer, M.C.; Bruchfeld, A.; Fabrizi, F.; Goldberg, D.S. KDIGO 2022 clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int.* **2022**, *102*, S129–S205. [CrossRef]
12. Alter, M.J.; Arduino, M.J.; Lyerla, H.C.; Miller, E.R.; Tokars, J.I. CDC Recommandations for preventing transmission of infecions among chronic hemodialysis patients. *MMWR Morb. Mortal. Wkly. Rep.* **2001**, *50*, 1–3.
13. Laporte, F.; Tap, G.; Jaafar, A.; Saune-Sandres, K.; Kamar, N.; Rostaing, L.; Izopet, J. Mathematical modeling of hepatitis C virus transmission in hemodialysis. *Am. J. Infect. Control* **2009**, *37*, 403–407. [CrossRef] [PubMed]
14. Jadoul, M. Transmission routes of HCV infection in dialysis. *Nephrol. Dial. Transplant.* **1996**, *11* (Suppl. S4), 36–38. [CrossRef] [PubMed]
15. Singh, S.; Facciorusso, A.; Loomba, R.; Falck-Ytter, Y.T. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. *Clin. Gastroenterol. Hepatol.* **2018**, *16*, 27–38.e4. [CrossRef]
16. Poynard, T.; Afdhal, N.H. Perspectives on Fibrosis Progression in hepatitis C: An à la Carte Approach to Risk Factors and Staging of Fibrosis. *Antivir. Ther.* **2010**, *15*, 281–291. [CrossRef]
17. Piedade, J.; Pereira, G.; Guimarães, L.; Duarte, J.; Victor, L.; Baldin, C.; Inacio, C.; Santos, R.; Chaves, Ú.; Nunes, E.P.; et al. Liver stiffness regression after sustained virological response by direct-acting antivirals reduces the risk of outcomes. *Sci. Rep.* **2021**, *11*, 11681. [CrossRef]
18. Li, J.; Gordon, S.C.; Rupp, L.B.; Zhang, T.; Boscarino, J.A.; Vijayadeva, V.; Schmidt, M.A.; Lu, M. The validity of serum markers for fibrosis staging in chronic hepatitis B and C. *J. Viral Hepat.* **2014**, *21*, 930–937. [CrossRef]
19. Davis, M.I.; Chute, D.F.; Chung, R.T.; Sise, M.E. When and how can nephrologists treat hepatitis C virus infection in dialysis patients? *Semin. Dial.* **2018**, *31*, 26–36. [CrossRef]

20. Cooke, G.S.; Andrieux-Meyer, I.; Applegate, T.L.; Atun, R.; Burry, J.R.; Cheinquer, H.; Dusheiko, G.; Feld, J.J.; Gore, C.; Griswold, M.G.; et al. Accelerating the elimination of viral hepatitis: A Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol. Hepatol.* **2019**, *4*, 135–184. [CrossRef]
21. World Health Organization (WHO). *Updated Recommandations on HCV Simplified Service Delivery and HCV Diagnostics: Policy Brief*; WHO: Geneva, Switzerland, 2022.
22. Kattakuzhy, S.; Gross, C.; Emmanuel, B.; Teferi, G.; Jenkins, V.; Silk, R.; Akoth, E.; Thomas, A.; Ahmed, C.; Espinosa, M.; et al. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers. *Ann. Intern. Med.* **2017**, *167*, 311. [CrossRef]
23. Rossaro, L.; Torruellas, C.; Dhaliwal, S.; Botros, J.; Clark, G.; Li, C.S.; Minoletti, M.M. Clinical Outcomes of Hepatitis C Treated with Pegylated Interferon and Ribavirin via Telemedicine Consultation in Northern California. *Dig. Dis. Sci.* **2013**, *58*, 3620–3625. [CrossRef] [PubMed]
24. Petrosillo, N.; Gilli, P.; Serraino, D.; Dentico, P.; Mele, A.; Ragni, P.; Puro, V.; Casalino, C.; Ippolito, G.; Collaborative Group. Prevalence of infected patients and understaffing have a rolein hepatitis C virus transmission in dialysis. *Am. J. Kidney Dis.* **2001**, *37*, 1004–1010. [CrossRef] [PubMed]
25. Shimokura, G.; Chai, F.; Weber, D.J.; Samsa, G.P.; Xia, G.; Nainan, O.V.; Tobler, L.H.; Busch, M.P.; Alter, M.J. Patient-Care Practices Associated with an Increased Prevalence of Hepatitis C Virus Infection among Chronic Hemodialysis Patients. *Infect. Control Hosp. Epidemiol.* **2011**, *32*, 415–424. [CrossRef] [PubMed]
26. Czarnecka, P.; Czarnecka, K.; Tronina, O.; Baczkowska, T.; Durlik, M. Utilization of HCV viremic donors in kidney transplantation: A chance or a threat? *Ren. Fail.* **2022**, *44*, 434–449. [CrossRef] [PubMed]
27. Biuletyn Poltransplant. Available online: https://www.poltransplant.org.pl/ (accessed on 31 January 2022). (In Polish).
28. Ros, R.L.; Kucirka, L.M.; Govindan, P.; Sarathy, H.; Montgomery, R.A.; Segev, D.L. Patient attitudes toward CDC high infectious risk donor kidney transplantation: Inferences from focus groups. *Clin. Transplant.* **2012**, *26*, 247–253. [CrossRef]

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Evaluation of Long-Term Outcomes of Direct Acting Antiviral Agents in Chronic Kidney Disease Subjects: A Single Center Cohort Study

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Abstract: Background: The chronic kidney disease (CKD) population, including kidney transplant recipients (KTRs) and subjects on renal replacement therapy, is particularly vulnerable to unfavorable outcomes from chronic hepatitis C (CHC). Currently, there are oral direct-acting antiviral agents (DAAs) available to eradicate the virus with favorable short-term outcomes; however, their long-term effects are lacking. The aim of the study is to assess the long-term efficacy and safety of DAA therapy in the CKD population. Methods: An observational, cohort single-center study was performed. Fifty-nine CHC subjects with CKD, treated with DAAs between 2016 and 2018, were enrolled in the study. Safety and efficacy profiles were assessed, including sustained virologic response (SVR), occult hepatitis C infection (OCI) incidence, and liver fibrosis. Results: SVR was achieved in 96% of cases (n = 57). OCI was diagnosed only in one subject following SVR. Significant liver stiffness regression was observed 4 years after SVR compared to baseline values (Mdn = 6.1 kPa, IQR = 3.75 kPa; 4.9 kPa, IQR = 2.9 kPa), $p < 0.001$. The most common adverse events were anemia, weakness, and urinary tract infection. Conclusion: DAAs provide a safe and effective cure for CHC in both CKD patients and KTRs with a favorable safety profile in the long-term follow-up.

Keywords: hepatitis C infection (HCV); chronic infection; liver fibrosis; direct-acting antiviral agents (DAA); occult hepatitis C infection; treatment efficacy; hemodialysis; kidney transplantation

Citation: Czarnecka, P.; Czarnecka, K.; Tronina, O.; Bączkowska, T.; Wyczałkowska-Tomasik, A.; Durlik, M.; Czerwinska, K. Evaluation of Long-Term Outcomes of Direct Acting Antiviral Agents in Chronic Kidney Disease Subjects: A Single Center Cohort Study. *J. Clin. Med.* **2023**, *12*, 3513. https://doi.org/10.3390/jcm12103513

Academic Editors: Hideaki Kato and Jun Li

Received: 4 May 2023
Accepted: 15 May 2023
Published: 17 May 2023

1. Introduction

Chronic hepatitis C (CHC) is a leading cause of liver-related diseases and mortality and a significant global health concern, affecting 71 million people worldwide [1]. CHC is far more prevalent in hemodialysis and kidney transplant recipients (KTRs) as compared to the general population [2]. In KTRs, the impact of CHC may even be more pronounced, given the permissive effect of immunosuppression on virus replication.

Furthermore, the concomitance of chronic kidney disease (CKD) and CHC results in higher liver-related mortality, diminished quality of life, and greater cardiovascular risk and adverse graft outcomes [3–5]. CHC triggers accelerated deterioration of kidney function in subjects with pre-existing CKD and may cause CKD itself [6,7]. Currently, marketed antiviral therapies (AVTs) facilitate safe and effective hepatitis C virus (HCV) eradication in the CKD population [8,9]. In their most recent guidelines, the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) recommend that all CKD subjects be considered for AVT [9,10]. Depending on the virus genotype and the advancement of both CKD and liver injury, CKD subjects may be offered grazoprevir in combination with elbasvir, glecaprevir with pibrentasvir, or sofosbuvir with velpatasvir.

The previous CHC interferon (IFN)-based therapies were neither effective nor well tolerated and have been successfully displaced with oral direct antiviral agents (DAAs) [11]. The advent of DAAs has revolutionized HCV treatment, with an efficacy of 94–97% [12]. Similar efficacy has been firmly established with short-term observation of the CKD population [13,14]. Despite immense advancement in the CHC treatment landscape, long-term outcomes following DAA treatment completion in the CKD population are lacking.

Successful HCV eradication does not unequivocally indicate that the subject is completely cured. While viral clearance prevents further liver injury, histological and biochemical alteration in the liver may persist. Furthermore, several studies suggested that DAAs may not entirely eliminate the virus despite sustained virologic response (SVR), and viral genetic material may be identified in certain reservoirs. This phenomenon was termed occult HCV infection (OCI), a cell-specific type of HCV infection diagnosed by the detection of HCV RNA in liver tissue or peripheral blood mononuclear cells (PBMCs) despite consecutively negative detection of HCV RNA in serum with high-sensitive assays [15]. Two types of OCI are defined in the literature, including HCV seronegative or HCV seropositive subjects, in whom the virus has been eradicated spontaneously or with AVT [16]. This study will refer only to the latter type of OCI.

Depending on the detection method, HCV genetic material may be present in up to 83% of the cases upon viral clearance [17], which might be a reservoir for relapse and viral transmission, as suggested in some studies [18,19]. Others demonstrated that OCI might be a root cause of cryptogenic liver disease and abnormal biochemical liver function despite SVR [20,21]. Since current data on the importance of OCI remain inconclusive, our study aims to evaluate the implication and prevalence of OCI following viral clearance in CKD subjects.

Undoubtedly, the primary goal of AVT therapy immediately after SVR is to prevent complications, which can be achieved by the prevention or regression of fibrosis. An increasing body of evidence revealed that a decline in liver stiffness (LS), to a certain extent, may be observed following successful HCV elimination [22]. Notably, liver fibrosis can be further utilized for the prognostication of adverse outcomes and patient mortality and may be perceived as an efficacy indicator of DAAs and a predictor of decompensation or hepatocellular carcinoma (HCC) occurrence in long-term follow-up [23,24].

Importantly, available studies have mostly documented a rapid decline in LS following SVR in a short time period; however, data beyond 12 months of observation are limited. It has been demonstrated that rapid fibrosis reversal measured with indirect fibrosis biomarkers might be overestimated, as it primarily stems from inflammation resolution, not the stiffness itself [25]. Therefore, it is important to verify the actual LS reduction that can be anticipated following AVT to accurately assess the long-term risk of CHC-related adverse outcomes.

LS may be evaluated using both direct and indirect methods. While liver biopsy remains the gold standard for liver fibrosis assessment, this method can be neither widely applied in clinical practice nor recommended in the HCV population for surveillance purposes owing to its invasive nature. Therefore, non-invasive indicators of fibrosis are often employed, including the aspartate aminotransferase-to-platelet ratio (APRI), the Fibrosis Index Based on 4 Factors (FIB-4), and FibroScan transient elastography. These indirect biomarkers are validated fibrosis indicators in the HCV population, which allow repeated evaluation over time [26,27].

CHC has been recognized as a major cause of HCC [28]. HCC develops primarily in cirrhotic patients, and HCV-related cirrhosis entails a greater HCC risk as compared to cirrhosis of any other etiologies. As such, HCC surveillance is imposed in subjects with advanced fibrosis (F3–F4), even after HCV elimination [9]. Initial studies suggested an association between DAAs and HCC development, which was not subsequently confirmed by several large-cohort studies [29–31]. Nevertheless, there is little doubt that the residual HCC risk persists after HCV eradication [32,33].

Until recently, CKD subjects were often left untreated despite the excellent efficacy of DAAs, as it was unclear whether new antiviral agents exacerbate kidney deficiency. Most recent studies showed that DAAs did not significantly impact kidney function or might even alleviate the decrease in estimated glomerular filtration rate (eGFR) in the CKD population upon SVR [34,35]. However, investigations of long-term kidney outcomes following SVR are limited.

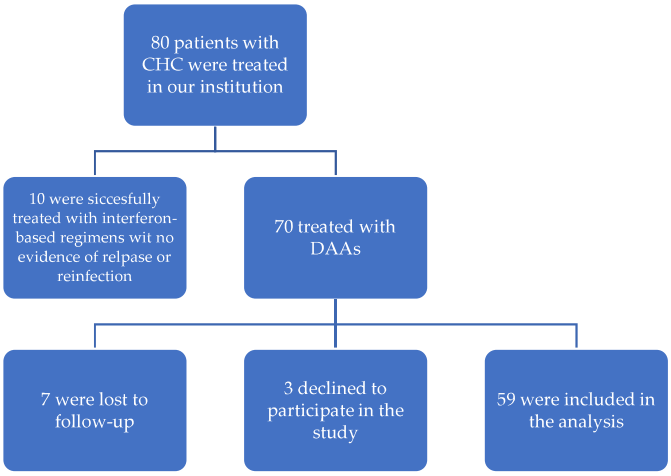
Evidence suggests that DAA treatment may trigger hepatitis B (HBV) reactivation even after AVT completion exists; therefore, HBV status needs to be established prior to DAA commencement [9,36,37]. Current HBV infection may require HBV nucleoside/nucleotide analog administration while receiving DAAs, whereas a history of HBV infection mandates close monitoring of alanine aminotransferase (ALT). Whenever ALT elevation persists after the end of treatment (EOT) or occurs during AVT, the subject needs to be tested for HBsAg and HBV DNA. Of note, patients on renal replacement therapy and KTRs are particularly vulnerable to HBV infection since HBV infection is far more prevalent in these subjects compared to the general population and often does not entail ALT elevation. Data on HBV reactivation in these populations are lacking.

To our best knowledge, this is the first study to report long-term data on fibrosis and kidney function assessment with a focus on the CKD population who receive IFN-sparing regimens. We consider this study of great importance as the CKD population is particularly vulnerable to unfavorable liver outcomes from CHC.

2. Materials and Methods

2.1. Study Population and Design

In this observational, single-center cohort study, all subjects with CHC and CKD (hemodialysis-dependent, KTRs, and ESRD), who underwent DAA therapy at our institution between 2016 and 2018 with valid FibroScan evaluation prior to DAA treatment and were able to provide written informed consent, were eligible for inclusion (Scheme 1). Subjects with coexisting HIV infection were excluded. Both treatment-naive and treatment-experienced patients were of interest. CHC was confirmed using HCV RNA polymerase chain reaction (PCR) detection (Cobas® AmpliScreen HCV v1.0 with the lower limit of detection of 15 IU/mL; Roche Diagnostics, Branchburg, NJ, USA) for at least 6 months. HCV genotyping was performed using the Linear Array Genotyping Test and Cobas® TaqMan® Qualitative test v1.0 with the lower limit of detection of 21 UI/mL (TaqMan; Roche Diagnostics, Branchburg, NJ, USA).



Scheme 1. Study population.

Data from medical records were obtained for concentrations of total bilirubin, aspartate aminotransferase (AST), ALT, and gamma-glutamyl transpeptidase (GGT) activity, albumin, and complete blood count, which were measured during routine outpatient visits before treatment, at EOT, and 1, 2, and 4 years after EOT. Similarly, indirect fibrosis biomarkers were evaluated, whereas FibroScan was conducted prior to AVT and at 4 years after EOT. Women of childbearing age were monitored with serum B-HCG while receiving DAAs. Kidney function was assessed by serum creatinine concentration (Scr) and eGFR estimated per the CKD Epidemiology Collaboration (CKD-EPI) equation. An allograft biopsy in KTRs was obtained whenever clinically indicated by the attending physician and assessed by the Banff criteria [38]. Data on AEs, CNI dose adjustments, and allograft biopsy reports were retrieved from medical records.

All subjects were screened for HCC with alfa-fetoprotein (AFP) and ultrasound examination prior to DAA commencement and remained under surveillance for HCC during the observation period. HBV status (HBsAg and anti-HBc) was established prior to DAA commencement, and anti-HBc-positive subjects were monitored monthly for HBV reactivation with ALT, HBsAg, and HBV DNA.

All SVR subjects had blood samples collected for OCI and underwent FibroScan transient elastography at 4 years after EOT. HCV RNA in PBMCs was tested in two consecutive samples, which were collected in intervals of 2–3 months.

AVT was based on DAAs with or without RBV. DAA therapy and its duration were guided by virus genotype, viral load (expressed as $\log_{10}$Iu/mL), kidney function, previous treatment status, liver disease severity, and DAA availability [39,40]. Detailed information on the use of AVT is available in Table 1.

The efficacy of DAA treatment was defined as SVR, which was determined by undetectable HCV RNA by PCR at 12 weeks after therapy completion. Patients who achieved SVR were re-tested for HCV RNA at the time of blood collection for PBMCs to discriminate between OCI and HCV reinfection.

All subjects provided informed consent form prior to study enrollment. The study was conducted in accordance with the provisions of the Declaration of Helsinki, and a favorable opinion of the Ethics Committee of the Medical University of Warsaw was obtained (KB/159/2019).

2.2. PBMC Isolation from Whole Blood

About 10 mL of whole blood was collected in a sterile EDTA-containing tube and diluted with NaCl (1:1). Immediately after collection, PBMCs were separated from whole blood with density gradient centrifugation and Ficoll Hypaque (Lonza, Verviers, Belgium) per manufacturer's instructions. Afterward, cells were washed three times with phosphate-buffered saline (PBS, pH 7.3 $\pm$ 0.1). The PBMCs were resuspended in RNALater solution (Ambion Inc., Austin, TX, USA) and stored at -80 °C for further analysis.

2.3. Detection of HCV RNA in PBMCs

HCV RNA was analyzed in PBMC with real-time PCR (RT-PCR) using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 (Roche Diagnostics, Basel, Switzerland) and COBAS TaqMan Analyzer COBAS AmpliPrep Instrument analyzer (Roche Diagnostics, Basel, Switzerland) according to three control levels: Roche Diagnostics COBAS TaqMan Negative Control, HCV Low Positive Control, and HCV High Positive Control. The assay was performed in a PBMCs sample volume of 500 µL per the manufacturer's recommendation. PBMC pellets were analyzed upon 1-min centrifugation at 3000 relative centrifugal force (rcf) with the Eppendorf Centrifuge 5424 (Eppendorf, Hamburg, Germany). HCV RNA concentration was automatically calculated using AMPLILINK 3.3.7 software (Roche Diagnostics, Basel, Switzerland).

Table 1. Baseline group characteristics.

Variable			N = 59
Sex			
	Male	N (%)	37 (62.7)
	Female	N (%)	22 (37.3)
Age, years		Mean (SD)	48.8 (13.1)
Concomitant disease			
Hypertension		N (%)	51 (86.4)
Diabetes		N (%)	21 (35.6)
Dyslipidemia		N (%)	32 (54.2)
Number of Ktx			
	1	N (%)	26 (44.1)
	2	N (%)	18 (30.5)
	3	N (%)	7 (11.9)
Genotype			
	1a	N (%)	2 (3.4)
	1b	N (%)	38 (64.4)
	3	N (%)	5 (8.5)
	4	N (%)	14 (23.7)
HCV viral load		Median (IQR)	1.97×10^6 (3.22×10^6)
Treatment status			
	Experienced	N (%)	12 (20.3)
	Naive	N (%)	47 (79.7)
DAA therapy used			
	Ombitasvir/parytaprevir/rytonavir	N (%)	14 (23.7)
	Ledipasvir/sofosbuvir	N (%)	31 (52.5)
	Glecaprevir/pibrentasvir	N (%)	3 (5.1)
	Elbasvir/grazoprevir	N (%)	11 (18.6)
	RBV	N (%)	45 (76.2)
Treatment duration			
	8 weeks	N (%)	2 (3.4)
	12 weeks	N (%)	49 (83.0)
	16 weeks	N (%)	2 (3.4)
	24 weeks	N (%)	6 (10.2)
Immunosuppression			
	CNI	N (%)	48 (81.4)
	MMF	N (%)	45 (76.3)
	GKS	N (%)	53 (89.9)
Time since Ktx and DAAs, years		Mean (SD)	11.18 (7.49)
BMI, kg/m^2		Mean (SD)	24.2 (4.3)
Past HBV infection			
	Yes	N (%)	23 (39.0)
	No	N (%)	36 (61.0)
ESRD			
	Glomerulonephritis	N (%)	24 (40.7)
	Unknown etiology	N (%)	7 (11.9)
	Hypertension	N (%)	3 (5.1)
	Diabetes	N (%)	8 (13.6)
	Vasculitis	N (%)	1 (1.7)
	Congenital urinary tract defect	N (%)	6 (10.2)
	Obstructive nephropathy	N (%)	4 (6.8)
	Chronic interstitial nephritis	N (%)	4 (6.8)
	HUS	N (%)	2 (3.4)
Fibrosis			
	LS, kPa	Median (IQR)	6.1 (3.75)
	F0–F1	N (%)	38 (64.4)
	F2	N (%)	10 (16.9)
	F3	N (%)	6 (10.2)
	F4	N (%)	5 (8.5)
	FIB-4	Median (IQR)	1.33 (1.3)
	APRI	Median (IQR)	2.76 (5.36)
	CAP, dB/m	Mean (SD)	231.19 (44.0)

APRI, aspartate aminotransferase-to-platelet ratio; BMI, body mass index; LS, liver stiffness; CAP, Controlled Attenuation Parameter; CNI, calcineurin inhibitors; DAA, direct oral antiviral agents; ESRD, end-stage renal disease; FIB-4, Fibrosis Index Based on 4 Factors; GKS, glucocorticosteroids; HBV, hepatitis B virus; HCV, hepatitis C virus; HUS, hemolytic uremic syndrome; IQR, interquartile range; Ktx, kidney transplantation; MMF, mycophenolate mofetil; RBV, ribavirin; SD, standard deviation.

2.4. Liver Fibrosis Assessment

LS was assessed with non-invasive biomarkers, such as APRI and FIB-4 scores, and transient elastography (FibroScan® Mini +430, Echosens, Paris, France). FibroScan was performed by a certified physician and graded per the Metavir scale as follows: F0–F1 ($\leq$7 kPa), F2 (7.1–9.4 kPa), F3 (9.5–12.4 kPa), and F4 ($\geq$12.5 kPa) [41]. Only FibroScan reports with at least 10 valid measurements, a success rate of at least 60%, and an interquartile range (IQR) < 0.3 were considered valid. LS was reported in the unit of kPa. Indirect fibrosis biomarkers, APRI [42] and FIB-4 [43], were computed based on the following equations:

$$\text{APRI} = (\text{AST [IU/L]}/\text{upper limit of the normal AST range*})/\text{platelet count [}10^9\text{/L]} \times 100$$

* the upper limit of normal AST range was 50 IU/L.

$$\text{FIB-4} = (\text{age [years]} \times \text{AST [IU/L]}/\text{platelet count [}10^9\text{/L]} \times \sqrt{\text{ALT [U/L]}})$$

2.5. Statistical Analysis

Analyses were conducted using the R Statistical language (version 4.1.1) on Windows 10 x64 (build 19044), using the packages effect size (version 0.6.0.1), sjPlot (version 2.8.9), report (version 0.5.1), ggstatsplot (version 0.9.0), and psych (version 2.1.6). The significance level of statistical tests in this analysis was set at $\alpha = 0.05$.

The normality of the variables was tested using the Shapiro–Wilk test. Additionally, measurements of asymmetry (skewness) and shape (kurtosis) were taken into account. Distributions in which skewness did not exceed 2.0 and kurtosis was below 7.0 were considered normal.

For non-parametric analyses of more than two groups, the Friedman rank sum test with Kendall's coefficient of concordance was used. For parametric analyses of more than two groups, Fisher's repeated measures one-way analysis of variance (ANOVA) with omega-squared effect size was conducted.

For analyses of two groups with a normally distributed variable, Student's *t*-test was used with the effect size calculated as Hedges' g. For variables without a normal distribution, the Wilcoxon test was applied with the estimation of a biserial rank correlation.

The correlation test statistics were based on Pearson's product-moment correlation coefficient and followed a *t* distribution with the length (x)−−2 degrees of freedom. An asymptotic confidence interval (CI) was given based on Fisher's *Z* transform.

The relationship between the nominal value and a continuous value was estimated with a point biserial correlation coefficient. Regression analysis in terms of cardinal and interval data was based on the linear model (GLMM).

2.6. Aim and Study Endpoints

This analysis aimed to assess the long-term efficacy and safety of DAAs in the CKD and end-stage renal disease (ESRD) population.

The primary study endpoints were SVR at 12 weeks following AVT cessation and OCI incidence following SVR, liver fibrosis estimated using FibroScan 4 years after SVR.

The secondary outcomes included renal function evaluated with Scr and eGFR, liver fibrosis estimated by indirect fibrosis biomarkers (APRI and FIB-4 scores), treatment-related adverse events (AEs), HCC incidence over a 4-year follow-up, HBV reactivation, liver function estimated using ALT, AST, and GGT, and the number of calcineurin inhibitor (CNI) dose adjustments.

3. Results

A total of 59 patients were enrolled (treatment-naive: 79.7%) with a mean age of 48.8 years (18–70 years) and a male ratio of 62.7% (n = 37). The study population consisted of 51 KTRs (all from deceased donors), 7 hemodialysis-dependent subjects, and 1 ESRD subject. The predominant HCV genotype was 1b (64.4%), followed by genotype 4 (23.7%). The median viral load was 1.97×10^6 (IQR: 3.22×10^6). The vast majority (64%) of the

subjects had F0–F1 fibrosis at baseline. The leading cause of ESRD was glomerulonephritis (40.7%). The mean time from kidney transplantation (KTx) to AVT commencement for KTRs was 11.18 years (standard deviation [SD]: 7.49 years). Most KTRs were maintained on a triple immunosuppressive scheme consisting of tacrolimus, mycophenolate mofetil, and prednisone. A history of HBV infection (hBsAg-, anti-HBc+) was present in 39% of the subjects. Patients were treated with IFN-sparing regimens (sofosbuvir-based: 52.6%, combined with rybavirin (RBV): 76.2%). AVT was administered for 8–24 weeks. Detailed baseline group characteristics are presented in Table 1.

3.1. SVR

SVR was achieved in 57/59 patients (96.6%). One patient without viral clearance (virus genotype 4) was on renal replacement therapy and was treatment-experienced (previously received pegylated IFN and simeprevir combined with RBV). The other one was a treatment-naive KTR with virus genotype 3. Both were men with baseline cirrhosis (F4) and suspected non-compliance (subjects did not recall the AVT schedule, and tablet counts significantly deviated from the prescribed frequency during follow-up visits). Excessive alcohol intake was confirmed later for both individuals. Following DAA failure, blood samples were collected and sent for analysis to identify any potential underlying resistant mutations that could have impacted unfavorable DAA outcomes. Results for both subjects were unremarkable for the resistance-associated NS5A mutations. No non-responders were retreated with DAAs due to active alcoholism. The first one died due to HCC and rapid progression of liver decompensation two years after AVT. The other subject died from a cardiovascular event one year after AVT.

3.2. Kidney Function

Scr remained stable for the duration of AVT and until 2 years after SVR. Overall, there was a significant increase in Scr 4 years after EOT (median: 1.47 mg/dL, IQR: 0.9 mg/dL) as compared to the baseline value (median: 1.34 mg/dL, IQR: 0.77 mg/dL) (χ^2_{Friedman} (4) = 10.88, p = 0.028, Figure 1). The effect size was slight per Landis's (1997) conventions. Kidney function deterioration was noted in 42.9% of the subjects (n = 21), whereas Scr improved at the 4-year observation timepoint in 32.6% of the subjects (n = 16) and remained intact in another 24.5% of the subjects (n = 12). Further details are provided in Figure 1.

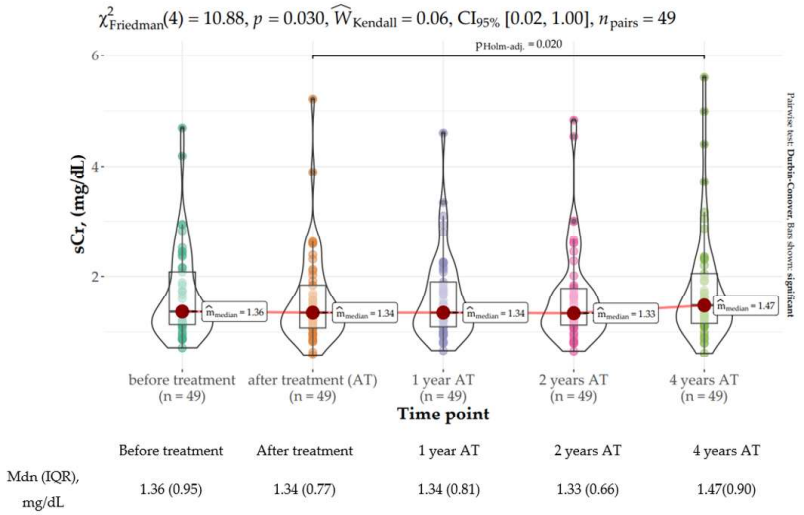


Figure 1. Distribution of serum creatinine concertation (mg/dL) at baseline, EOT (end of treatment), and 1, 2, and 4 years following sustained virologic response (SVR).

Similarly, kidney function delineated by the mean eGFR was comparable while on AVT. Nevertheless, Fisher's repeated measures one-way ANOVA revealed that eGFR gradually declined over time upon SVR, reaching a statistically significant decrease at 4 years after SVR (mean: 57.61 mL/min/1.73 m^2, SD: 25.41 mL/min/1.73 m^2 vs. mean: 51.41 mL/min/1.73 m^2, SD: 24.43 mL/min/1.73 m^2) (F_{Fisher} [3.24, 155.51] = 4.12, p = 0.006, Figure 2). The effect size was very small per Field's (2013) conventions. The most prominent decline of 4.55 mL/min/1.73 m^2 was observed between the second and fourth years of observation.

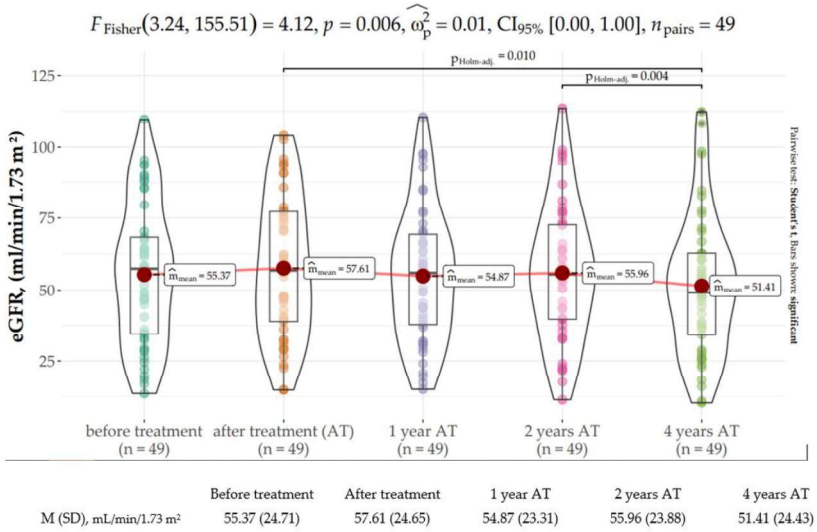


Figure 2. Distribution of the estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR).

3.3. Liver Function

ALT sharply declined at EOT as compared to the baseline value (median: 20 U/I, IQR: 7.5 U/I vs. median: 40 U/I, IQR: 42.5 U/I; $p < 0.001$) and further decreased until one year after EOT (median: 14 U/I, IQR: 9 U/I; $p < 0.001$). After one year, ALT plateaued within the range of normality (see Table 2). Consistently, AST and GGT markedly declined after treatment and remained within the range of normality thereafter (see Table 2).

Table 2. Distribution of liver function tests at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR).

Variable	Before Treatment	After Treatment	1 Year AT	2 Years AT	4 Years AT
ALT Mdn (IQR), U/I	40.0 (40.0)	20.0 (8.0)	14.0 (9.0)	15.0 (7.0)	15 (9.0)
AST Mdn (IQR), U/I	33.0 (24.0)	19.0 (11.0)	20.0 (7.0)	19.0 (6.0)	18.0 (8.0)
GGT Mdn (IQR), U/I	61.0 (72.0)	27.0 (27.0)	24.0 (22.0)	28.0 (23.0)	26.0 (18.0)

The V Wilcoxon test for dependent variables revealed that LS significantly improved 4 years following SVR as compared to the baseline value (median: 6.1 kPa, IQR: 3.75 kPa vs. median: 4.9 kPa, IQR: 2.9 kPa) (V Wilcoxon 1500, $p < 0.001$ with strong correlation coefficient, Figure 3). Two subjects who did not achieve SVR were not available for LS assessment at the 4-year time point.

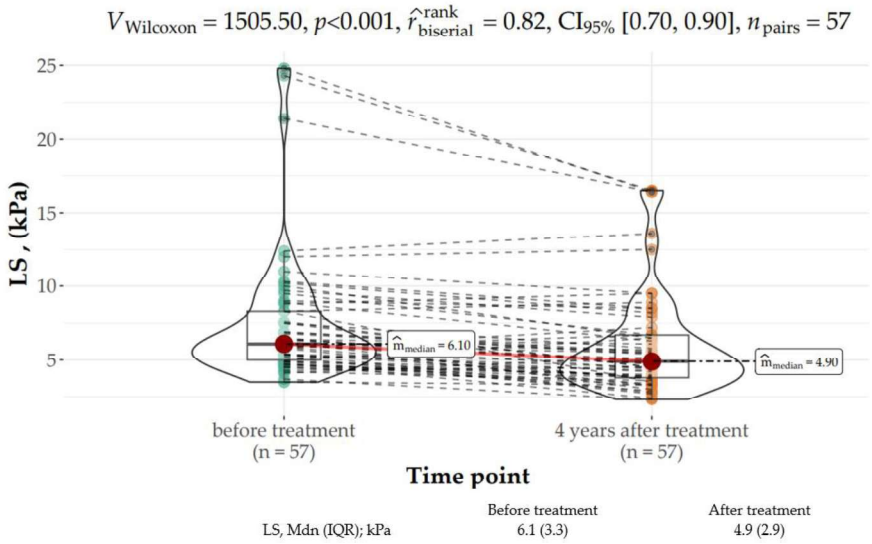


Figure 3. Distribution of LS (kPa) parameters at baseline and 4 years after the end of treatment (EOT).

The Friedman rank sum test showed a statistically significant difference between the baseline FIB-4 score (median: 1.29, IQR: 1.3) with the EOT score (median: 0.97, IQR: 0.82) as well as the score at two years after treatment (median: 1.21, IQR: 1.07) ($\chi^2_{Friedman}$ (4) = 31.85, p < 0.001). The effect size was slight per Landis's (1997) conventions (Figure 4).

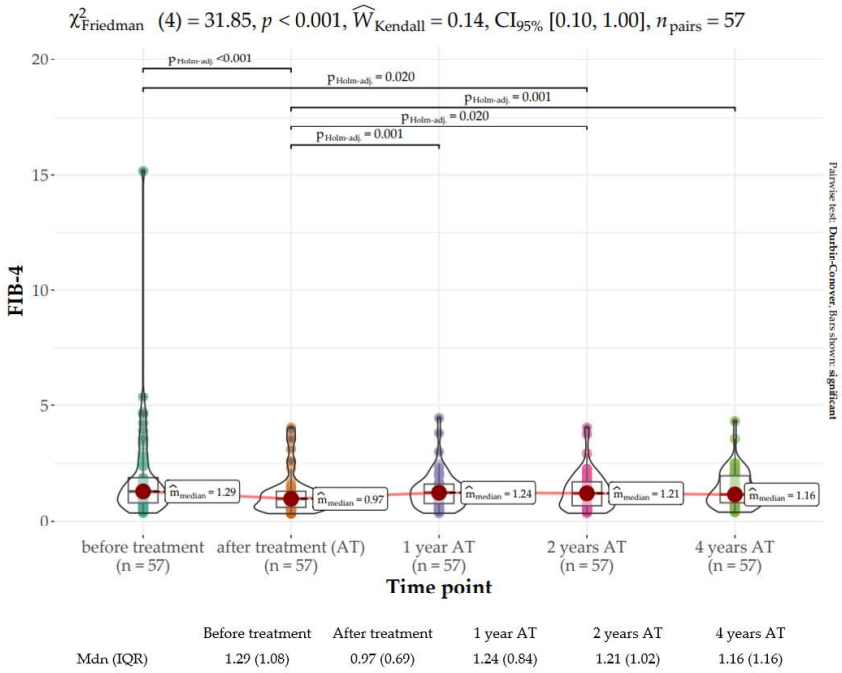


Figure 4. Distribution of the Fibrosis Index Based on 4 Factors (FIB-4) score at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR).

The FIB-4 score at EOT was significantly lower than those at later time points. The scores of the remaining time points after treatment did not differ significantly from each other and were in the range of 1.16–1.24.

The APRI score notably improved from baseline (median: 2.76, IQR: 5.36) to EOT (median: 0.23, IQR: 0.12) and plateaued within the range of 0.23–0.24 thereafter ($\chi^2_{Friedman}$ (4) = 99.37, $p < 0.001$). The effect size was moderate per Landis's (1997) conventions (Figure 5).

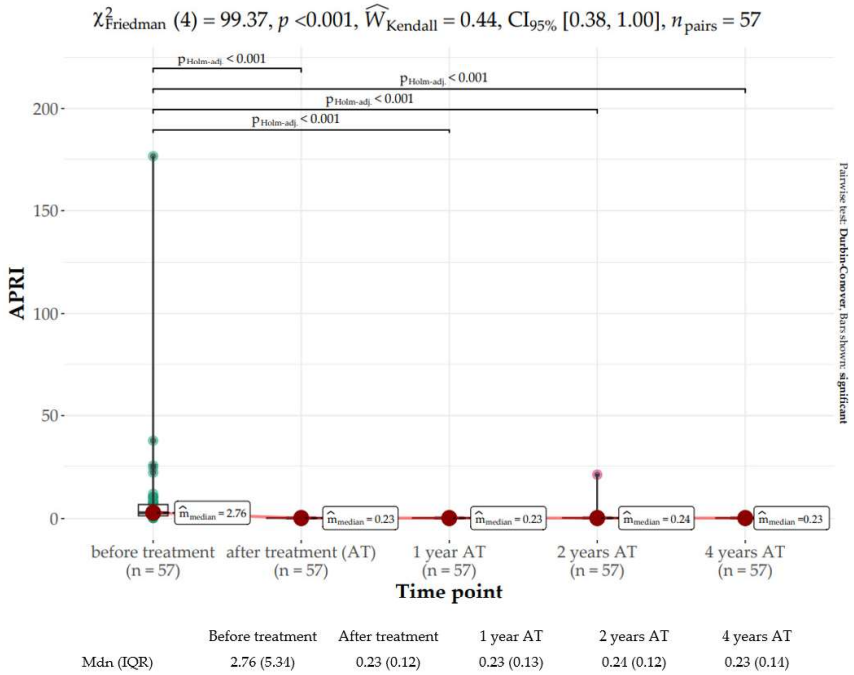


Figure 5. Distribution of the aspartate aminotransferase-to-platelet ratio (APRI) score at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR).

Both APRI (r = 0.53, $p < 0.001$) and FIB-4 (r = 0.70; $p < 0.001$) scores were strongly correlated with fibrosis measured with FibroScan transient elastography before AVT initiation. However, at the 4-year observation time point, only APRI (r = 0.33, $p = 0.013$) score, but not the FIB-4 score (r = 0.25, $p = 0.063$), showed a moderate correlation.

Neither genotype nor liver fibrosis at baseline impacted liver fibrosis stiffness regression. Only in treatment-experienced patients, a greater liver fibrosis reversal of 1.24 (CI: −2.27 to −0.21, $p = 0.020$) was observed. Further details are provided in Figure 6.

At the 4-year time point, the percentage of subjects with advanced fibrosis (F3–F4) estimated per FibroScan was reduced from 19.83% (n = 11) to 12.3% (n = 7). While fibrosis was not downgraded in any cirrhosis patients, this parameter was downgraded to F2 or even F1 at the end of the follow-up in four patients with advanced fibrosis (F3). In one subject with advanced fibrosis, this condition had progressed to cirrhosis based on FibroScan measurements (baseline vs. 4 years after EOT: 12.4 kPa vs. 13.6 kPa). Further details are provided in Figure 7.

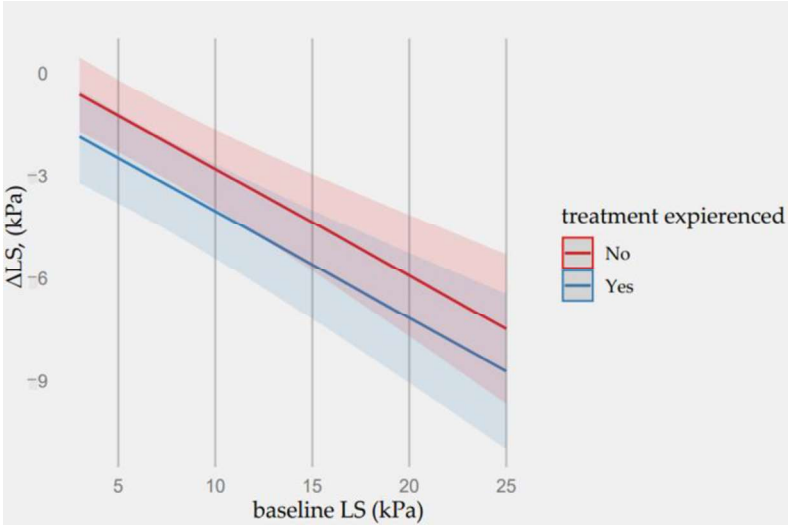


Figure 6. Predictions of ΔE values from the fitted regression model based on baseline LS concentration and patient's treatment-experienced factor.

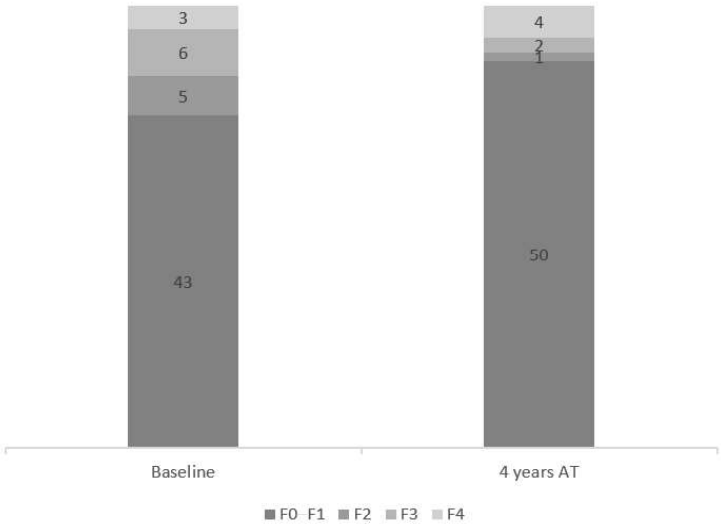


Figure 7. Fibrosis distribution at baseline and at 4 years after end of treatment (EOT).

3.4. CNI Dose Adjustments

CNI was administered to 81.4% of the study subjects. All subjects had their CNI dose reduced prior to AVT commencement whenever ritonavir was used. No immunosuppression dose adjustments were required for 24.5% of the patients, whereas more than 20% of the patients required more than 2 CNI dose adjustments during DAA therapy.

3.5. Safety

Overall, 102 AEs were observed, with the majority being mild to moderate in intensity. The most commonly reported AEs were anemia (25.4%), weakness (22%), and urinary tract infection (UTI, 22%). UTI was not considered AVT-related. Anemia was observed only in RBV-treated subjects. Twenty-one subjects (19.1%) did not experience any AEs. Serious

AEs (SAEs) requiring hospitalization were reported for eight patients. The vast majority (n = 5) was due to UTI, followed by pneumonia and atrial fibrillation. No SAEs were considered AVT-related or resulted in treatment discontinuation. Detailed information on AEs is present in Table 3.

Table 3. Adverse events.

Adverse Event		N = 59
Anemia	N (%)	15 (25.4%)
Weakness	N (%)	13 (22%)
Urinary tract infection	N (%)	13 (22%)
Sterile leukocyturia	N (%)	8 (13.6%)
Upper respiratory tract infection	N (%)	7 (11.9%)
Headache	N (%)	4 (6.8%)
Diarrhea	N (%)	3 (5.1%)
Hypertransaminasemia	N (%)	3 (5.1%)
Pneumonia	N (%)	3 (5.1%)
Abdominal pain	N (%)	2 (3.4%)
Ankle edema	N (%)	2 (3.4%)
Worsening of blood pressure control	N (%)	2 (3.4%)
Herpes	N (%)	2 (3.4%)
Fatigue	N (%)	2 (3.4%)
Worsening of exercise tolerance	N (%)	1 (1.7%)
Bone pains	N (%)	1 (1.7%)
Distal deep vein thrombosis	N (%)	1 (1.7%)
Nausea	N (%)	1 (1.7%)
Sleep disturbance	N (%)	1 (1.7%)
Hematuria	N (%)	1 (1.7%)
Weight loss	N (%)	1 (1.7%)
Syncope	N (%)	1 (1.7%)
Hyperkalemia	N (%)	1 (1.7%)
Gout	N (%)	1 (1.7%)
Sinusitis	N (%)	1 (1.7%)
Hypotension	N (%)	1 (1.7%)
Fistulae	N (%)	1 (1.7%)
Atrial fibrillation	N (%)	1 (1.7%)
Inflammatory fistula tumor	N (%)	1 (1.7%)
Otitis	N (%)	1 (1.7%)
Pruritus	N (%)	1 (1.7%)

During the study, renal biopsy was clinically indicated in one subject while on DAAs. The biopsy report was indicative of acute antibody-mediated rejection (ABMR). This 32-year-old male patient, for whom DAA was initiated at 6 months after KTx, had biopsy-proven ABMR prior to HCV treatment. As such, AMBR was not considered treatment-induced.

No HBV reactivation was noted during the observation period.

HCC was observed in two subjects, including one who did not achieve SVR. The subject, who was successfully treated for CHC, had genotype 3; and a single HCC lesion was diagnosed in segment VII 6 months after EOT despite no evidence of HCC prior to DAA initiation. He had F3 fibrosis at baseline, and no liver fibrosis regression was observed with both serum fibrosis biomarkers and liver elastography. He was successfully treated for HCC with tumorectomy and remained in the follow-up with no evidence of HCC recurrence.

3.6. OCI

HCV was detected in PBMCs only in one subject and in both samples. This patient was a treatment-experienced 28-year-old man after 3 KTx with virus genotype 1b, who was on a triple immunosuppressive scheme with sofosbuvir-based regimens and RBV. He did

not have any evidence of liver injury, his ALT was within the normal range, and HCV RNA was undetectable in serum 4 years following EOT. Regardless of OCI, fibrosis regression was observed in this patient from 5.4 kPa to 2.8 kPa, and there was no evidence of HCC during the observation period.

3.7. Long-Term Outcomes of DAAs in Kidney Transplant Recipients

The Friedman rank sum test revealed that the FIB-4 score significantly declined between baseline (median = 1.38, IQR = 1.42) and EOT (median = 1.10, IQR = 0.81) and then gradually increased over time, reaching median = 1.25, IQR = 1.16 four years after EOT (χ^2_{Friedman} (4) = 31.85, $p < 0.001$). The effect size was slight, as per Landis's (1997) conventions (see Figure S1).

Similarly, a notable change in APRI score was noted between baseline (median = 3.12, IQR = 5.57) and EOT (median = 0.24, IQR = 0.12) χ^2_{Friedman} (4) = 86.45, $p < 0.001$, and plateaued within the rage of 0.23–0.24. The effect size was moderate, as per Landis's (1997) conventions (see Figure S2).

The *V* Wilcoxon test for dependent variables revealed a significant difference in *LS* before treatment (median = 6.05 kPa, IQR = 3.75 kPa) and four years after treatment (median = 4.80 kPa, IQR = 277 kPa), $V_{Wilcoxon}$= 1200.50, p <0.001 with strong correlation coefficient (see Figure S3).

ALT rapidly declined at EOT when compared to the baseline value (median = 40.50 U/I, IQR = 47.75 U/I vs. median = 20.50 U/I, IQR = 7.75 U/I; $p < 0.001$) and further decreased until one year after EOT (median = 15.00, IQR = 8.75; $p < 0.001$). After one year, ALT plateaued within the range of normality (Figure S4). Consistently, AST and GGT markedly declined after treatment and remained within the range of normality thereafter (Figures S5 and S6).

4. Discussion

The present study demonstrated that DAAs were highly effective and well-tolerated in both ESRD patients and KTRs, with the SVR rate exceeding 96%. This finding is congruent with those from previously published studies in CKD cohorts [13,14].

Further, OCI infection was infrequent in the CKD population following SVR, and no adverse clinical implications of HCV RNA in PBMCs were detected. Despite having detectable HCV RNA in PBMCs, the only OCI-positive subject had fibrosis reversal by 48% at the 4-year follow-up time point with no evidence of viral relapse. Lybeck et al. demonstrated a similarly low OCI incidence during their long-term follow-up study [44]. However, they did not observe fibrosis alleviation when OCI was diagnosed. Since the OCI subject in our analysis had milder fibrosis as estimated with FibroScan, we speculated that his condition was more likely reversible. Furthermore, unlike Lybeck et al., who examined the long-term impact of IFN-based agents, we analyzed the impact of DAAs on fibrosis; there is current evidence suggesting that greater fibrosis regression may be anticipated after DAAs as compared to IFN-based therapies [22,45]. Despite the advocacy against the clinical implication of OCI in our study, its results need to be interpreted with caution, given the small sample size, and further studies are needed to elucidate these findings.

Further, the OCI incidence in our study may be underestimated, as PBMCs might reveal only up to 61% of the OCI cases as compared to liver biopsy [46]. Given the invasive nature of the biopsy with limited benefit for the subject, we decided against this method of OCI detection for our study purpose. In the literature, OCI incidence following SVR varied, with ranges of 0–50% in PBMCs and 0–83% in liver tissue [17]. Discrepancies in OCI incidence may stem from differences in detection methods among the studies. A uniform approach for OCI detection would be important to determine the true incidence rate and implication following SVR.

The present study demonstrated the long-term effectiveness of DAA. Fibrosis decline was documented with both FibroScan transient elastography and indirect serum biomarkers. Four years after AVT cessation, fibrosis regression by 20%, as estimated with FibroScan, was observed. However, SVR could not be identified with complete cure as

advanced fibrosis or cirrhosis was still present in as much as 12% of the subjects after EOT. In other studies, higher LS decline was observed in the general population [22,33,45]. Facciorusso et al. documented an LS decline of 46% at 5 years in 83 DAA responders, whereas Flisiak et al. documented an LS decline exceeding 30% at 5 years [33,45]. Importantly, their data referred to the general population and could not be easily applied to the CKD population. Additionally, the majority of the population in our study comprised KTRs, with CNI, MMF, and GKS being the most prevalent immunosuppressive regimens. Since CNIs and MMF are known to exert profibrotic properties, we may speculate that immunosuppressive treatment could have contributed to the lower regression of LS [47–49]. Additional studies are needed to prognosticate the extent to which fibrosis regression could be anticipated after SVR in CKD subjects.

Interestingly, the only predictor of greater LS decline was treatment-experienced status. However, among the group with available paired LS measurements, fibrosis was lower at baseline, and two subjects from this group did not reach SVR. Therefore, this finding needs to be interpreted with caution. Previous studies also aimed to identify potential predictors of fibrosis decline. Both host factors, such as the presence of liver cirrhosis, old age of the patient, alcohol consumption, diabetes mellitus or BMI, and viral factors (genotype, viral load) were investigated, but the results remained inconclusive [50,51].

Even though non-invasive fibrosis indices decreased significantly after DAA therapy, they only showed a moderate correlation with FibroScan results, which might translate to lesser reliability for follow-up purposes after SVR. Przekop et al. observed that the correlation between fibrosis estimated with indirect serum biomarkers and FibroScan decreased after treatment [52]. Similar observations have been previously noted in HBV subjects [53]. Since both FIB-4 and APRI scores include the ALT value in their formulas, these scores may automatically decline with the reduction in inflammation despite the persistence of fibrosis, which may explain the weaker correlation with FibroScan following SVR.

In our analysis, both Scr and eGFR remained intact at EOT. Moreover, no acute kidney injury (AKI) incidence was observed during AVT. Since on-treatment raw creatinine values were not collected for the purpose of this analysis, we could not exclude eGFR fluctuations. This finding is supported by a recent analysis by Sulkowski et al., who demonstrated that even sofosbuvir-based AVT, which was considered nephrotoxic until recently, did not have an adverse impact on kidney function [54].

Furthermore, in our study, one year after EOT, kidney function progressively deteriorated, reaching a statistically significant decline at the 4-year observation time point. This progressive decline in kidney function was similarly reported in other studies, such as Saxena et al. [55]. While available analysis showed relatively stable kidney function in terms of AVT, most studies were of limited follow-up duration, and the long-term effects of AVT have not been fully elucidated [56–59].

In our study, the most prominent decline in eGFR was observed between the 2- and 4-year observation time points. Importantly, the vast majority of our patients comprised KTRs, with an average duration of 11 years from KTx until DAA commencement. Since it has been previously documented that kidneys from deceased donors last an average of 12 years, we may presume that the observed kidney function deterioration was rather a result of kidney allograft lifespan triggered by AVT [60]. Nevertheless, it is not surprising that kidney biomarkers may deteriorate during follow-up due to the progressive nature of CKD. Furthermore, a retrospective observational cohort study by Sise et al. demonstrated that AVT might not prevent eGFR decline entirely in the CKD population but only slow down CKD progression [34]. Nevertheless, it has been firmly established that SVR conferred a survival benefit in dialysis patients and reduced ESRD risk, which are of greater importance than eGFR. Additional studies are needed to evaluate eGFR dynamics following DAA beyond one year of observation.

DAAs were well-tolerated, and only a limited number of AEs were reported during AVT. Acute rejection was also infrequent and considered not AVT-related. The most commonly reported AEs were RBV-induced anemia, weakness, and UTI. Nevertheless,

no red blood cell transfusion was required, and RBV dose reduction or discontinuation was needed in all subjects receiving RBV. Likewise, RBV reduction was clinically indicated in other studies [61]. The vast majority of our study population comprised KTRs, and it has been previously documented that infections are the most prevalent complication following KTx, with UTI being the most frequent. No UTIs were AVT-related. Furthermore, interactions with CNIs could be limited under the current CHC treatment landscape with the use of pan-genetic DAA regimens. Since RBV is rarely added to the AVT scheme, we might assume that AEs might even be less frequent [8].

Genotype 3 is considered more difficult to treat when compared to the remaining genotypes, as it entails a greater risk of virologic failure [39]. In our study, 4 out of 5 patients with genotype 3 achieved SVR. The one who did not was suspected of non-compliance, as described above.

The present study has some limitations. First, the study was of a retrospective nature with a small sample size. Additionally, prescribed CHC agents at the time when the study was conducted are not in line with the most recent recommendations. Moreover, there is a lack of consistency among CHC therapies used and histological validation of fibrosis assessments, which were measured with indirect fibrosis indices. However, the completeness of data and long-term follow-up period are some definite strengths of our study.

Despite the great achievement in the field of HCV eradication, there are still many challenges ahead, including the goal of HCV elimination by 2030, variations in medication availability among different countries, and high treatment costs.

5. Conclusions

DAAs provided a safe and effective cure for CHC in both CKD patients and KTRs with a favorable safety profile. Long-term liver fibrosis regression might be obtained with AVT. There was no evidence of OCI in CKD subjects and KTRs following SVR. Longitudinal studies are needed to establish whether post-SVR liver regression translates to mortality and morbidity benefit.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12103513/s1. Figure S1: Distribution of the FIB-4 parameter at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR) in kidney transplant recipients; Figure S2: Distribution of APRI parameter at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR) in kidney transplant recipients; Figure S3: Distribution of LS (kPa) parameters at baseline and 4 years after the end of treatment (EOT) in kidney transplant recipients; Figure S4: Distribution of alanine aminotransferase (ALT, U/L) at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR) in kidney transplant recipients.; Figure S5: Distribution of aspartate aminotransferase (AST, U/L) at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR) in kidney transplant recipients.; Figure S6: Distribution of gamma-glutamyl transferase (GGT, U/L) at baseline, end of treatment (EOT), and 1, 2, and 4 years following sustained virologic response (SVR) in kidney transplant recipients. Also can be found in 10.17632/n3w628yk3t.1.

Author Contributions: Conceptualization, P.C., O.T.; methodology, P.C., A.W.-T.; formal analysis, P.C. and K.C. (Kinga Czarnecka); writing—original draft preparation, P.C.; writing—review and editing, O.T., M.D.; visualization, K.C. (Katarzyna Czerwinska); supervision, T.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Warsaw (KB/159/2019), date of approval 4 November 2019.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting the results reported in the article can be found under the following DOI: 10.17632/8yrhk6gv8n.1.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Blach, S.; Zeuzem, S.; Manns, M.; Altraif, I.; Duberg, A.-S.; Muljono, D.H.; Waked, I.; Alavian, S.M.; Lee, M.-H.; Negro, F.; et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *Lancet Gastroenterol. Hepatol.* **2017**, *2*, 161–176. [CrossRef] [PubMed]
2. Fissell, R.B.; Bragg-Gresham, J.L.; Woods, J.D.; Jadoul, M.; Gillespie, B.; Hedderwick, S.A.; Rayner, H.C.; Greenwood, R.N.; Akiba, T.; Young, E.W. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: The DOPPS. *Kidney Int.* **2004**, *65*, 2335–2342. [CrossRef] [PubMed]
3. Pol, S.; Parlati, L.; Jadoul, M. Hepatitis C virus and the kidney. *Nat. Rev. Nephrol.* **2019**, *15*, 73–86. [CrossRef]
4. Fabrizi, F.; Dixit, V.; Messa, P. Impact of hepatitis C. on survival in dialysis patients: A link with cardiovascular mortality? *J. Viral Hepat.* **2012**, *19*, 601–607. [CrossRef] [PubMed]
5. Fabrizi, F.; Messa, P.; Martin, P. Health-Related Quality of Life in Dialysis Patients with HCV Infection. *Int. J. Artif. Organs* **2009**, *32*, 473–481. [CrossRef] [PubMed]
6. Fabrizi, F.; Donato, F.M.; Messa, P. Association Between Hepatitis C Virus and Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Ann. Hepatol.* **2018**, *17*, 364–391. [CrossRef] [PubMed]
7. Fabrizi, F.; Verdesca, S.; Messa, P.; Martin, P. 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. [CrossRef]
8. Jadoul, M.; Awan, A.A.; Berenguer, M.C.; Bruchfeld, A.; Fabrizi, F.; Goldberg, D.S.; Jia, J.; Kamar, N.; Mohamed, R.; Pol, S.; et al. KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. *Kidney Int.* **2022**, *102*, S129–S205. [CrossRef]
9. Pawlotsky, J.M.; Negro, F.; Aghemo, A.; Berenguer, M.; Dalgard, O.; Dusheiko, G.; Marra, F.; Puoti, M.; Wedemeyer, H. EASL recommendations on treatment of hepatitis C: Final update of the series. *J. Hepatol.* **2020**, *73*, 1170–1218. [CrossRef]
10. Ghany, M.G.; Morgan, T.R. Hepatitis C. Guidance 2019 Update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology* **2020**, *71*, 686–721. [CrossRef]
11. Fabrizi, F.; Martin, P.; Dixit, V.; Messa, P. Hepatitis C Virus Infection and Kidney Disease: A Meta-Analysis. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 549–557. [CrossRef] [PubMed]
12. Ahmed, H.; Abushouk, A.I.; Menshawy, A.; Mohamed, A.; Negida, A.; Loutfy, S.A.; Abdel-Daim, M.M. Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin for Treatment of Hepatitis C Virus Genotype 1: A Systematic Review and Meta-analysis. *Clin. Drug. Investig.* **2017**, *37*, 1009–1023. [CrossRef] [PubMed]
13. Roth, D.; Nelson, D.R.; Bruchfeld, A.; Liapakis, A.; Silva, M.; Monsour, H.; Martin, P.; Pol, S.; Londoño, M.C.; Hassanein, T.; et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): A combination phase 3 study. *Lancet* **2015**, *386*, 1537–1545. [CrossRef]
14. Gane, E.; Lawitz, E.; Pugatch, D.; Papatheodoridis, G.; Bräu, N.; Brown, A.; Pol, S.; Leroy, V.; Persico, M.; Moreno, C.; et al. Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment. *N. Engl. J. Med.* **2017**, *377*, 1448–1455. [CrossRef]
15. Castillo, I.; Pardo, M.; Bartolomé, J.; Ortiz-Movilla, N.; Rodríguez-Iñigo, E.; de Lucas, S.; Salas, C.; Jiménez-Heffernan, J.A.; Pérez-Mota, A.; Graus, J.; et al. Occult Hepatitis C Virus Infection in Patients in Whom the Etiology of Persistently Abnormal Results of Liver-Function Tests Is Unknown. *J. Infect. Dis.* **2004**, *189*, 7–14. [CrossRef] [PubMed]
16. Welker, M.W.; Zeuzem, S. Occult hepatitis C: How convincing are the current data? *Hepatology* **2009**, *49*, 665–675. [CrossRef] [PubMed]
17. Attar, B.M.; Van Thiel, D. A New Twist to a Chronic HCV Infection: Occult Hepatitis C. *Gastroenterol. Res. Pract.* **2015**, *2015*, 579147. [CrossRef]
18. Austria, A.; Wu, G.Y. Occult Hepatitis C Virus Infection: A Review. *J. Clin. Transl. Hepatol.* **2018**, *6*, 155–160. [CrossRef]
19. Castillo, I.; Bartolomé, J.; Quiroga, J.A.; Barril, G.; Carreño, V. Hepatitis C virus infection in the family setting of patients with occult hepatitis C. *J. Med. Virol.* **2009**, *81*, 1198–1203. [CrossRef]
20. Wang, Y.; Rao, H.; Chi, X.; Li, B.; Liu, H.; Wu, L.; Zhang, H.; Liu, S.; Zhou, G.; Li, N.; et al. Detection of residual HCV-RNA in patients who have achieved sustained virological response is associated with persistent histological abnormality. *EBioMedicine* **2019**, *46*, 227–235. [CrossRef]
21. Pardo, M.; López-Alcorocho, J.M.; Rodríguez-Iñigo, E.; Castillo, I.; Carreño, V. Comparative study between occult hepatitis C virus infection and chronic hepatitis C. *J. Viral Hepat.* **2007**, *14*, 36–40. [CrossRef] [PubMed]
22. Singh, S.; Facciorusso, A.; Loomba, R.; Falck-Ytter, Y.T. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. *Clin. Gastroenterol. Hepatol.* **2018**, *16*, 27–38.e4. [CrossRef] [PubMed]
23. Poynard, T.; Afdhal, N.H. Perspectives on Fibrosis Progression in Hepatitis C: An à la Carte Approach to Risk Factors and Staging of Fibrosis. *Antivir. Ther.* **2010**, *15*, 281–291. [CrossRef]

24. Piedade, J.; Pereira, G.; Guimarães, L.; Duarte, J.; Victor, L.; Baldin, C.; Inacio, C.; Santos, R.; Chaves, Ú.; Nunes, E.P.; et al. Liver stiffness regression after sustained virological response by direct-acting antivirals reduces the risk of outcomes. *Sci. Rep.* **2021**, *11*, 11681. [CrossRef] [PubMed]
25. Hsu, W.-F.; Lai, H.-C.; Su, W.-P.; Lin, C.-H.; Chuang, P.-H.; Chen, S.-H.; Chen, H.Y.; Wang, H.W.; Huang, G.T.; Peng, C.Y. Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents. *BMC Gastroenterol.* **2019**, *19*, 63. [CrossRef] [PubMed]
26. Holmberg, S.D.; Lu, M.; Rupp, L.B.; Lamerato, L.E.; Moorman, A.C.; Vijayadeva, V.; Boscarino, J.A.; Henkle, E.M.; Gordon, S.C.; Chronic Hepatitis Cohort Study (CHeCS) Investigators. Noninvasive Serum Fibrosis Markers for Screening and Staging Chronic Hepatitis C Virus Patients in a Large US Cohort. *Clin. Infect. Dis.* **2013**, *57*, 240–246. [CrossRef]
27. Li, J.; Gordon, S.C.; Rupp, L.B.; Zhang, T.; Boscarino, J.A.; Vijayadeva, V.; Schmidt, M.A.; Lu, M.; Chronic Hepatitis Cohort Study (CHeCS) Investigators. The validity of serum markers for fibrosis staging in chronic hepatitis B and C. *J. Viral Hepat.* **2014**, *21*, 930–937. [CrossRef]
28. Axley, P.; Ahmed, Z.; Ravi, S.; Singal, A.K. Hepatitis C Virus and Hepatocellular Carcinoma: A Narrative Review. *J. Clin. Transl. Hepatol.* **2018**, *6*, 79–84. [CrossRef]
29. Kozbial, K.; Moser, S.; Schwarzer, R.; Laferl, H.; Al-Zoairy, R.; Stauber, R.; Stättermayer, A.F.; Beinhardt, S.; Graziadei, I.; Freissmuth, C.; et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. *J. Hepatol.* **2016**, *65*, 856–858. [CrossRef]
30. Waziry, R.; Hajarizadeh, B.; Grebely, J.; Amin, J.; Law, M.; Danta, M.; George, J.; Dore, G.J. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol.* **2017**, *67*, 1204–1212. [CrossRef]
31. Mittal, S.; El-Serag, H.B.; Sada, Y.H.; Kanwal, F.; Duan, Z.; Temple, S.; May, S.B.; Kramer, J.R.; Richardson, P.A.; Davila, J.A. Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans Is Associated With Nonalcoholic Fatty Liver Disease. *Clin. Gastroenterol. Hepatol.* **2016**, *14*, 124–131.e1. [CrossRef] [PubMed]
32. Ioannou, G.N.; Beste, L.A.; Green, P.K.; Singal, A.G.; Tapper, E.B.; Waljee, A.K.; Sterling, R.K.; Feld, J.J.; Kaplan, D.E.; Taddei, T.H.; et al. Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients with Baseline Cirrhosis or High FIB-4 Scores. *Gastroenterology* **2019**, *157*, 1264–1278.e4. [CrossRef] [PubMed]
33. Flisiak, R.; Zarębska-Michaluk, D.; Janczewska, E.; Łapiński, T.; Rogalska, M.; Karpińska, E.; Mikuła, T.; Bolewska, B.; Białkowska, J.; Flejscher-Stępniewska, K.; et al. Five-Year Follow-Up of Cured HCV Patients under Real-World Interferon-Free Therapy. *Cancers* **2021**, *13*, 3694. [CrossRef] [PubMed]
34. Sise, M.E.; Chute, D.F.; Oppong, Y.; Davis, M.I.; Long, J.D.; Silva, S.T.; Rusibamayila, N.; Jean-Francois, D.; Raji, S.; Zhao, S.; et al. Direct-acting antiviral therapy slows kidney function decline in patients with Hepatitis C virus infection and chronic kidney disease. *Kidney Int.* **2020**, *97*, 193–201. [CrossRef]
35. Huang, C.-F.; Tseng, K.-C.; Cheng, P.-N.; Hung, C.-H.; Lo, C.-C.; Peng, C.-Y.; Bair, M.J.; Yeh, M.L.; Chen, C.H.; Lee, P.L.; et al. Impact of Sofosbuvir-Based Direct-Acting Antivirals on Renal Function in Chronic Hepatitis C Patients With Impaired Renal Function: A Large Cohort Study From the Nationwide HCV Registry Program (TACR). *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 1151–1162.e6. [CrossRef]
36. Potthoff, A.; Berg, T.; Wedemeyer, H. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon-a2b and ribavirin. *Scand. J. Gastroenterol.* **2009**, *44*, 1487–1490. [CrossRef]
37. Wang, C.; Ji, D.; Chen, J.; Shao, Q.; Li, B.; Liu, J.; Wu, V.; Wong, A.; Wang, Y.; Zhang, X.; et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. *Clin. Gastroenterol. Hepatol.* **2017**, *15*, 132–136. [CrossRef]
38. Haas, M.; Sis, B.; Racusen, L.C.; Solez, K.; Glotz, D.; Colvin, R.B.; Castro, M.C.; David, D.S.; David-Neto, E.; Bagnasco, S.M.; et al. Banff 2013 Meeting Report: Inclusion of C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arterial Lesions. *Am. J. Transplant.* **2014**, *14*, 272–283. [CrossRef]
39. Pawlotsky, J.M.; Negro, F.; Aghemo, A.; Berenguer, M.; Dalgard, O.; Dusheiko, G.; Marra, F.; Puoti, M.; Wedemeyer, H. EASL Recommendations on Treatment of Hepatitis C 2018. *J. Hepatol.* **2018**, *69*, 461–511. [CrossRef]
40. Halota, W.; Flisiak, R.; Juszczyk, J.; Małkowski, P.; Pawłowska, M.; Simon, K.; Tomasiewicz, K. Recommendations by Polish Group of Experts for HCV for the treatment of viral hepatitis C in 2018. *Hepatologia* **2018**, *18*, 1–9. [CrossRef]
41. Castéra, L.; Vergniol, J.; Foucher, J.; Le Bail, B.; Chanteloup, E.; Haaser, M.; Darriet, M.; Couzigou, P.; De Lédinghen, V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* **2005**, *128*, 343–350. [CrossRef] [PubMed]
42. Wai, C. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* **2003**, *38*, 518–526. [CrossRef] [PubMed]
43. Vallet-Pichard, A.; Mallet, V.; Nalpas, B.; Verkarre, V.; Nalpas, A.; Dhalluin-Venier, V.; Fontaine, H.; Pol, S. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology* **2007**, *46*, 32–36. [CrossRef] [PubMed]
44. Lybeck, C.; Brenndörfer, E.D.; Sällberg, M.; Montgomery, S.M.; Aleman, S.; Duberg, A.-S. Long-term follow-up after cure from chronic hepatitis C virus infection shows occult hepatitis and a risk of hepatocellular carcinoma in noncirrhotic patients. *Eur. J. Gastroenterol. Hepatol.* **2019**, *31*, 506–513. [CrossRef] [PubMed]

45. Facciorusso, A.; Del Prete, V.; Turco, A.; Buccino, R.V.; Nacchiero, M.C.; Muscatiello, N. Long-term liver stiffness assessment in hepatitis C virus patients undergoing antiviral therapy: Results from a 5-year cohort study. *J. Gastroenterol. Hepatol.* **2018**, *33*, 942–949. [CrossRef]
46. Castillo, I.; Bartolomé, J.; Quiroga, J.A.; Barril, G.; Carreño, V. Diagnosis of occult hepatitis C without the need for a liver biopsy. *J. Med. Virol.* **2010**, *82*, 1554–1559. [CrossRef]
47. Lim, E.J.; Chin, R.; Nachbur, U.; Silke, J.; Jia, Z.; Angus, P.W.; Torresi, J. Effect of Immunosuppressive Agents on Hepatocyte Apoptosis Post-Liver Transplantation. *PLoS ONE.* **2015**, *10*, e0138522. [CrossRef]
48. Frizell, E.; Abraham, A.; Doolittle, M.; Bashey, R.; Kresina, T.; Van Thiel, D.; Zern, M.A. FK506 Enhances fibrogenesis in in vitro and in vivo models of liver fibrosis in rats. *Gastroenterology* **1994**, *107*, 492–498. [CrossRef]
49. Berenguer, M.; Schuppan, D. Progression of liver fibrosis in post-transplant hepatitis C: Mechanisms, assessment and treatment. *J. Hepatol.* **2013**, *58*, 1028–1041. [CrossRef]
50. Elsharkawy, A.; Samir, R.; El-Kassas, M. Fibrosis regression following hepatitis C antiviral therapy. *World J. Hepatol.* **2022**, *14*, 1120–1130. [CrossRef]
51. Cheng, C.-H.; Chu, C.-Y.; Chen, H.-L.; Lin, I.T.; Wu, C.H.; Lee, Y.K.; Hu, P.J.; Bair, M.J. Direct-acting antiviral therapy of chronic hepatitis C improves liver fibrosis, assessed by histological examination and laboratory markers. *J. Formos. Med. Assoc.* **2021**, *120*, 1259–1268. [CrossRef] [PubMed]
52. Przekop, D.; Klapaczynski, J.; Grytczuk, A.; Gruszewska, E.; Gietka, A.; Panasiuk, A.; Golaszewski, S.; Cylwik, B.; Chrostek, L. Non-Invasive Indirect Markers of Liver Fibrosis after Interferon-Free Treatment for Hepatitis C. *J. Clin. Med.* **2021**, *10*, 3951. [CrossRef] [PubMed]
53. Kim, W.R.; Berg, T.; Asselah, T.; Flisiak, R.; Fung, S.; Gordon, S.C.; Janssen, H.L.; Lampertico, P.; Lau, D.; Bornstein, J.D.; et al. Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. *J. Hepatol.* **2016**, *64*, 773–780. [CrossRef]
54. Sulkowski, M.; Telep, L.E.; Colombo, M.; Durand, F.; Reddy, K.R.; Lawitz, E.; Bourlière, M.; Cheinquer, N.; Scherbakovsky, S.; Ni, L.; et al. Sofosbuvir and risk of estimated glomerular filtration rate decline or end-stage renal disease in patients with renal impairment. *Aliment. Pharmacol. Ther.* **2022**, *55*, 1169–1178. [CrossRef] [PubMed]
55. Saxena, V.; Koraishy, F.M.; Sise, M.E.; Lim, J.K.; Schmidt, M.; Chung, R.T.; Liapakis, A.; Nelson, D.R.; Fried, M.W.; Terrault, N.A.; et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int.* **2016**, *36*, 807–816. [CrossRef] [PubMed]
56. Medeiros, T.; Rosário, N.F.; Saraiva, G.N.; Andrade, T.G.; Silva, A.A.; Almeida, J.R. Renal safety after one year of sofosbuvir-based therapy for chronic hepatitis C: A Brazilian "real-life" study. *J. Clin. Pharm. Ther.* **2018**, *43*, 707–713. [CrossRef]
57. Liu, C.-H.; Lee, M.-H.; Lin, J.-W.; Liu, C.-J.; Su, T.-H.; Tseng, T.-C.; Chen, P.J.; Chen, D.S.; Kao, J.H. Evolution of eGFR in chronic HCV patients receiving sofosbuvir-based or sofosbuvir-free direct-acting antivirals. *J. Hepatol.* **2020**, *72*, 839–846. [CrossRef]
58. Tronina, O. Real-world direct-acting antiviral treatment in kidney transplant and hemodialysis patients: The EpiTer-2 multicenter observational study. *Ann. Gastroenterol.* **2021**, *34*, 438–446. [CrossRef]
59. Driedger, M.; Galanakis, C.; Cooper, C. Direct acting antiviral HCV treatment does not influence renal function. *Medicine* **2020**, *99*, e20436. [CrossRef]
60. Poggio, E.D.; Augustine, J.J.; Arrigain, S.; Brennan, D.C.; Schold, J.D. Long-term kidney transplant graft survival—Making progress when most needed. *Am. J. Transplant.* **2021**, *21*, 2824–2832. [CrossRef]
61. Sawinski, D.; Kaur, N.; Ajeti, A.; Trofe-Clark, J.; Lim, M.; Bleicher, M.; Goral, S.; Forde, K.A.; Bloom, R.D. Successful Treatment of Hepatitis C in Renal Transplant Recipients with Direct-Acting Antiviral Agents. *Am. J. Transplant.* **2016**, *16*, 1588–1595. [CrossRef] [PubMed]

Opinia Komisji Bioetycznej

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KB/...159.../2019

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 04 listopada 2019 r. po zapoznaniu się z wnioskiem:

Lek.Paulina Czarnecka,
Klinika Medycyny Transplantacyjnej ,Nefrologii
i Chorób Wewnętrznych,
ul. Nowogrodzka 59, 02-006 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.: „Ocena skuteczności i bezpieczeństwa leczenia przewlekłego wirusowego zapalenia wątroby typu C w schemacie bezinterferonowym u pacjentów z przewlekłą chorobą nerek (hemodializowanych i po przeszczepieniu nerki) w obserwacji długoterminowej ."

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

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Warszawa, dnia 08 listopada 2021r.

AKBE/ 205 / 2021

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 08 listopada 2021 r. przyjęła do wiadomości informację na temat badania pt:" Leczenie przewlekłego wirusowego zapalenia wątroby typu C u pacjentów dializowanych w dobie terapii bezinterferonowych." Wyżej wymienione badanie jest zgodne z zasadami etyki badań naukowych.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie.

WARSZAWA 13.11.23
(miejscowość, data)

MAGDALENA DUBLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników i pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej
(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 13.11.23
(miejscowość, data)

KINGA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

.....

zbieranie piśmiennictwa, pisanie pracy

.....

Mój udział procentowy w przygotowaniu publikacji określam jako...3... %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako..90.. %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....

(imię i nazwisko kandydata do stopnia)

Czarnecka Kinga
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 03.11.23
(miejscowość, data)

OLGA TROKIMA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

.....

Interpretacja wyników, autor merytoryczny

.....

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 90 %,

obejmował on: koncepcja pracy, wybór metodyki badawczej, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 4.12.2023
(miejscowość, data)

TERESA BACZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Utilization of HCV viremic donors in kidney transplantation: a chance or a threat?" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Konsultacja i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 90 %,

obejmował on: koncepcja pracy, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej
(imię i nazwisko kandydata do stopnia)

Teresa Baczkowska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 03.11.23
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Interpretacja wyników, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcja pracy, postawienie hipotez, wybór metodyki badawczej, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 21.11.23
(miejscowość, data)

WERONIKA ZARYCHTA-WIŚNIEWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A Na ional Cross-Sectional Survey. ” oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Promotorstwo badania

Mój udział procentowy w przygotowaniu publikacji określam jako 0,6 %.
Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcja pracy, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

Zarychta-Wiśniewska Weronika
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 13.11.23
(miejscowość, data)

KINGA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Are We on the Right Track fc · HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Wybór metodyki badania, interpretacja wyników

Mój udział procentowy w przygotowaniu publikacji określam jako 0,2 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: Koncepcja badania, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

Czarnecka Kinga

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 21.11.23
(miejscowość, data)

MAGDALENA DURLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacje oraz nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 0,1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcję badania, postawienie hipotez, wybór metodyki badania, interpretację wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 4.12.2023
(miejscowość, data)

TERESA BAŃCZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Are We on the Right Track for HCV Micro-Elimination? HCV Management Practices in Dialysis Centers in Poland—A National Cross-Sectional Survey " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacje i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 0,1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 95 %,

obejmował on: koncepcja pracy, powstawanie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....
(imię i nazwisko kandydata do stopnia)

Teresa Bańczkowska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 13.11.23
(miejscowość, data)

ALEKSANDRA WYCZAŁKOWSKA-TOMASIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Wybór metodyki badań

Mój udział procentowy w przygotowaniu publikacji określam jako 0,5 %.
Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 90 %,

obejmował on: koncepcję pracy, powstanie hipotez, wybór metodyki badań, przeprowadzenie badania, interpretację wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

Aleksandra Wyczałkowska-Tomasik
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 13.11.23
(miejscowość, data)

OLGA TRONINA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja pracy i postawienie hipotez, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 90 %,

obejmował on: koncepcja pracy i postawienie hipotez, wybór metodyki badań, prowadzenie badania, interpretacje wyników i pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 13.11.23
(miejscowość, data)

KATARZYNA CZERWIŃSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Graficzne przedstawienie wyników, zbieranie danych

Mój udział procentowy w przygotowaniu publikacji określam jako 0,5 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: Koncepcja pracy, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....

(imię i nazwisko kandydata do stopnia)

Katarzyna Czerwińska
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 13.11.23
(miejscowość, data)

TERESA BAŚCZKOWSKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

konsultacje i nadzór merytoryczny

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako 80 %,

obejmował on: koncepcja badania, postawienie hipotez, wybór metodyki badania, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....

(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa 13.11.23
(miejscowość, data)

MAGDALENA DURLIK
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Nadzór merytoryczny, korekta pracy przed złożeniem do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określ am jako 80 %,

obejmował on: koncepcję badania, powstawanie hipotez, wybór metodyki badania, interpretację wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej

(imię i nazwisko kandydata do stopnia)

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

WARSZAWA 13.11.23
(miejscowość, data)

KINGA CZARNECKA
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „ Evaluation of long-term outcomes of direct acting antiviral agents in chronic kidney disease subjects: a single center cohort study. " oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Interpretacja danych

Mój udział procentowy w przygotowaniu publikacji określam jako. 2 %.

Wkład Pauliny Czarneckiej w powstawanie publikacji określam jako. 90 %,

obejmował on: koncepcja badania, postawienie hipotez, wybór metodyki badań, interpretacja wyników, pisanie pracy

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Pauliny Czarneckiej.....

(imię i nazwisko kandydata do stopnia)

Czarnecka Kinga

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników