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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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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.