Clinical Study

Eradication of HCV in Renal Transplant Recipients and Its Effects on Quality of Life

Massimo Sabbatini,1 Ivana Capuano,1 Silvia Camera,2 Lucia Ferreri,1 Pasquale Buonanno,3 Laura Donnarumma,2 Nicola Caporaso,2 and Filomena Morisco2

1Dipartimento di Salute Pubblica, Università degli Studi Federico II di Napoli, Italy
2Dipartimentodi Medicina Clinica e Chirurgia, Università degli Studi Federico II di Napoli, Italy
3Dipartimento di Scienze Riproduttive ed Odontostomatologiche, Università degli Studi Federico II di Napoli, Italy

Correspondence should be addressed to Massimo Sabbatini; sabbatin@unina.it

Received 7 May 2018; Accepted 14 August 2018; Published 30 August 2018

Academic Editor: Maria Irene Bellini

Copyright © 2018 Massimo Sabbatini et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. The use of direct antiviral agents (DAA) has radically modified the course of HCV hepatitis in renal patients. Aim of this study was to assess the effects of HCV eradication on quality of life (QOL) in renal transplant recipients (RTR), measured by CLDQ and SF-36.

Methods. Sixteen RTR with well preserved GFR (mean: 60.3±19.3 ml/min) and chronic HCV infection with moderate liver stiffness (9.3±1.7 kPa) were given a sofosbuvir-based regimen for 12 weeks and had a 1 year follow-up. Results. At end of treatment (EOT) a complete viral clearance was observed in all the patients, with normalization of most laboratory data and a consistent reduction in liver stiffness. All these parameters remained stable after 1 year, as well as renal function and proteinuria. Questionnaire data showed consistent amelioration in different “emotional” domains at EOT, which persisted after 1 year and were associated with a globally improved QOL, although there was no change in most of the “physical” domains in both questionnaires. One patient under ribavirin developed an acute anemia and withdrew from the study, but no further adverse episode was observed throughout the study. Conclusions. Our data, while confirming the efficacy of oral DAA, show that HCV infection represents a heavy psychological burden in renal transplant recipients, greatly alleviated by viral eradication, which determines a significant improvement in QOL that represents an important outcome in management of all transplant recipients. This trial is registered with ISRCTN97560076.

1. Background

Chronic hepatitis by C virus infection (HCV) is a significant public health problem with a worldwide estimated prevalence of 3% [1], consistently higher in patients with chronic kidney disease (CKD), either in conservative and substitutive treatment [2]. In renal transplant recipients (RTR), HCV infection is associated with a significantly higher risk for all-cause mortality and graft loss compared to the uninfected counterpart [1, 3] and represents a serious trouble for these patients, due to the negative impact of immunosuppression on disease progression and its effect on the outcome of their graft, as a consequence of increased incidence of diabetes, enhanced onset of cardiovascular diseases, easier recurrence of glomerulonephritis, and faster progression of chronic allograft nephropathy [4–8]. The recent introduction of second-generation direct antiviral agents (DAA) has dramatically changed the therapeutic scenario of HCV infection in general population, as well as in renal patients [9, 10], and mostly in RTR, in whom interferon-based regimens are contraindicated because of the risk of acute graft rejection [8]; indeed, these new regimens have evidenced an optimal response in terms of either viral clearance or patients’ tolerability [2, 11–18].

Given the high impact of HCV infection on patients’ quality of life (QOL) in general population [19], the aim of the present study was to evaluate the effects of HCV eradication on health-related QOL in RTR, commonly affected by a heavy...
clinical and psychological burden. Today, improvements in QOL represent a widely accepted measure of treatment outcome in any chronic disease, since patients require greater attention to their physical and emotional well-being in everyday life.

To this extent a small cohort of RTR underwent a 12-week sofosbuvir-based regimen and was prospectively followed up for one year, with repeated evaluation of QOL questionnaires. Our working hypothesis was that eradication of HCV may determine consistent improvements in QOL.

2. Materials and Methods

2.1. Patients. This case series consisted of 16 HCV-infected kidney transplant recipients in regular follow-up at our Nephrology and Kidney Transplant Unit, referred to our hepatologists (NC, FM), who selected the proper DAA combination on the basis of HCV genotype and estimated glomerular filtration rate (eGFR) and drug availability in Italy at time of starting treatment. Our transplant recipients were white-Caucasian, all being first transplant from cadaver donors (two with simultaneous renal and liver transplantation).

The first 10 patients enrolled in the study were selected among RTR in regular follow-up at the Day Hospital of Renal Transplantation of University Federico II of Naples, on the basis of specific criteria suggested by Italian Ministry of Health in September 2015. They were as follows: age ≥18 years; presence of HCV-antibodies and of HCV-RNA replication, independently of liver enzymes alteration; a liver stiffness value ≥7 kPa at transient elastography (TE); presence of HCV genotype 1, 2, 3, or 4; and stable renal function in the last 6 months, with an estimated glomerular filtration rate (eGFR) >35 ml/min and no graft rejection in the preceding 12 months. From September 2016 DAA treatment could be started also in patients with lower TE values, and 6 further patients were enrolled. Exclusion criteria were as follows: decompensated liver cirrhosis, chronic B-hepatitis or human immunodeficiency virus infection, and presence of specific intercurrent clinical problems, like infections or ESA-resistant anemia.

2.2. Treatment. Antiviral therapy consisted of sofosbuvir (400 mg/day) in all patients, associated with daclatasvir (60 mg/day; n=9), ledipasvir (90 mg/day; n=2), ribavirin (weight-based dosage; n=2), or velpatasvir (100 mg, n=2); one patient was under sofosbuvir + ledipasvir + ribavirin. The addition of ribavirin and of its discontinuation was at the discretion of hepatologist. Treatment lasted 12 weeks, like in general population, and its efficacy was evaluated by monitoring viral load at baseline, after 4, 8, and 12 weeks of treatment (end of treatment, EOT), and 12 and 48 weeks after EOT. Liver stiffness was evaluated by TE [FibroScan; Touch 5.02; Echosens; France] at baseline, at EOT, and 48 weeks after EOT by a skilled operator (SC), on the basis of current guidelines. Maintenance immunosuppression therapy consisted of a calcineurin inhibitor (CNI) in 12 patients (5 on tacrolimus and 7 on cyclosporine) in conjunction with steroids (n=9), mycophenolic acid derivatives (n=6), and sirolimus (n=2). Four patients were treated with sirolimus in association with steroids (n=4) and mycophenolic acid derivatives (n=2). In all the patients, induction therapy consisted of Basiliximab (20 mg, during surgery and at the 4th postoperative day).

2.3. Quality of Life Measurement. All the patients were administered the Chronic Liver Disease questionnaire (CLDQ) and the Short Form Health Survey (SF-36) questionnaire during their clinical visits, i.e., before starting the therapy (Basal), at the end of therapy (EOT), and 48 weeks later (1 year). CLDQ is the first disease specific instrument developed to evaluate health-related quality of life (QOL) in patients with liver disease [20] which includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. The answers to each question are graded with scores ranging from 0 (best option) to 6 (worst option), according to its Italian version [21]: high scores denote a worse liver-related quality of life.

Health-related QOL was evaluated using the Italian version of SF-36. This tool contains one item that evaluates the perceived changes in health status, while the remaining 35 items are used to generate eight subscales, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0–100 scale on the assumption that each question carries equal weight; the lower scores reflect greater disability. The eight sections are general health perception, physical functioning, role limitation due to poor physical health, role limitation due to poor emotional health, social role functioning, bodily pain, emotional well-being, and vitality. Both questionnaires were given and explained to patients in the early morning of the scheduled visit by their trained caregiver (IC) and were completed at her presence after the visit.

2.4. Laboratory Data. Trough levels of tacrolimus, cyclosporine, and sirolimus were monitored every week during DAA administration and every 4 weeks later on by commercial immunoassays. Estimated-GFR (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). Urinary protein excretion was measured on 24-hour urine samples.

All laboratory values were determined by standard methods. Plasma HCV mRNA levels were measured by a real-time PCR-based method (Abbott Real Time, Lower Limit of Quantification: 12 IU/ml).

2.5. Statistical Analysis. Data were first analyzed with Shapiro’s test to determine their distribution. Parametric data were presented as mean and standard deviation; nonparametric data were presented as median and range. Parametric data were analyzed with repeated measures ANOVA or Student’s t test for paired data, as appropriate; nonparametric data analysis was performed by Friedman’s test. Post hoc analysis was conducted by Bonferroni’s test for parametric data and Dunn’s test for nonparametric data. Differences were considered statistically significant if p<0.05. Data were analyzed using statistical software R (R version 3.3.3).
Table 1: Patient characteristics at baseline (n=16).

| Demographic characteristics | Baseline laboratory values |
|-----------------------------|-----------------------------|
| Age, y                      | 64 (26-71) a                |
| Sex (M/F)                   | 11/5                        |
| Time from RTX to HCV therapy, mo | 150.9 (84.4) b          |

| Cause of end-stage renal disease | |
|----------------------------------|-----------------------------|
| Vesicoureteral reflux            | 1                           |
| Chronic glomerulonephritis       | 6                           |
| Others or unknown                | 9                           |

| HCV genotype: | Baseline laboratory values |
|--------------|-----------------------------|
| 1a           | 47.5 (16-306) a             |
| 1b           | 30.2 (11-137) a             |
| 2            | 31.4 (17-85) a              |
| 4            | 95.1 (41.3) b               |

Data are expressed as median (range) a or mean (standard deviation) b. Abbreviations. eGFR: estimated glomerular filtration rate; GGT: γ-glutamyl-transpeptidase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AFP: alpha fetoprotein (0-4 IU/ml).

The study was approved by Ethical Committee of “Federico II” University (#290/15). At time of starting treatment, all the patients were adequately informed about the potential adverse effects of DAAs and their possible interactions with immunosuppressive drugs; all the patients gave their informed written consent. Data were collected from October 2015 to February 2018.

3. Results

Baseline patients’ demographic and clinical data are summarized in Table 1. Six patients had a FibroScan value >10 kPa at time of starting therapy. All the patients had documented HCV infection prior to transplantation and received HCV-negative organs. Their median HCV-RNA concentration was 2.1E6 (4.1E5-1.3E7) log 10 IU/mL, and a viral load greater than 800,000 IU/mL was present in 14 patients. Mean plasma concentrations of liver enzymes were in the upper zone of normal ranges.

The etiology of renal disease was undetermined in 57% of patients; six patients had biopsy proven glomerular diseases (2 focal and segmental glomerular sclerosis, 1 IgA-nephropathy, 1 postinfectious, and 2 not defined), and proteinuria exceeded 1 g/24 hours in 2 patients; 3 patients were affected by posttransplant diabetes (one insulin-dependent). One patient withdrew from the study during the 4th week of treatment because of acute anemia and his data are not considered in statistics; the remaining 15 patients completed at least 1-year follow-up. At baseline, no correlation was detected between FibroScan values, viral load, and liver enzymes (P=0.14).

3.1. Effects of DAA on HCV Infection. A complete viral clearance, i.e., undetectable HCV-RNA replication, was observed in all the patients at EOT. It was associated with a significant decrease of GGT, AST, and ALT values (-60%, -49%, and -57%, respectively, versus Basal), with no change in alkaline phosphatase nor in total bilirubin (Figure 1); these parameters remained stable throughout the follow-up. Interestingly, also FibroScan values were consistently reduced at EOT (-33%) and were not modified thereafter (Figure 2), implying that no further improvement was obtained in the medium term.
Despite a better functioning liver. No change was detected in hemoglobin, albumin, and glucose plasma levels throughout the study (data not shown).

3.2. Effects of DAA on Renal Function. DAA administration did not affect renal function. No change, in fact, was observed in mean eGFR at EOT (59.9±16.8 versus 60.3±19.3 ml/min in Basal, NS) nor after the 1-year follow-up (56.0±19.9 ml/min, NS), although two patients had developed an important impairment of eGFR (-31% and -49%, versus respective Basal). Similarly, proteinuria values remained quite stable throughout the observation period, averaging 0.58±0.76 g/24hrs at Basal, 0.55±0.77 at EOT, and 0.47±0.88 after 1 year (NS). Indeed, we observed an improvement in urinary protein excretion in 7/15 patients (with complete disappearance of proteinuria in 3 patients) and a clear worsening in the 2 patients who developed the renal impairment.

Trough levels of CNI were slightly reduced (tacrolimus, -24%; cyclosporine, -11%), and mild adjustments of drug doses were necessary in 3 patients. Sirolimus plasma concentrations, conversely, remained stable. Daily doses of mycophenolic acid and steroids were not changed during the study. The need for recombinant erythropoietin support or treatment of established diabetes also remained unchanged during therapy.

3.3. Quality of Life. HCV eradication was associated with a better QOL. At baseline, median value of CLDQ was 2.89 (range: 1.18-5.36), which denotes a relatively preserved liver-related quality of life. All the domains tended to be lower at EOT, although not significantly, with the exception of “activity”. At completion of the 1-year observation period (Figure 3), a consistent and significant decrease was recorded in global score, whose median value decreased by 36% (p<0.01 versus Basal), following the significant improvements observed in “worry”, “emotional function”, and perceived “abdominal symptoms”. Conversely, the domains of “fatigue”, “systemic symptoms”, and “activity” were not affected by HCV infection recovery.

The results of SF-36 questionnaire are reported in Table 2. It is interesting to note that both the scores of the “emotional well-being” and of the “role limitation due to emotional problems” were already significantly higher at EOT and further improved after 1 year, where also the perception of a beneficial “health change” was described, associated with a better perception of patient’s social role. Interestingly, like in CLDQ, physical functioning and role limitation due to physical problems or vitality were marginally affected by DAA treatment.

3.4. DAA Side Effects. One patient developed a symptomatic episode of acute anemia during the 4th week of treatment with sofosbuvir + ribavirin (nadir of hemoglobin: 6.6 g/dl), which required hospitalization, transfusion of 2 blood units, and DAA withdrawal; the patient refused a new treatment with different drugs. Throughout the entire study, tolerance to treatment was excellent: mild headache (n=2) and fatigue (n=3) were the most common reported side effects, requiring no therapy. No acute graft rejection or infectious episode occurred in any patient, and after the initial decline, trough levels of immunosuppressive drugs remained stable during the follow-up period.

4. Discussion

In this paper we describe our single-center experience with a 12-week course of DAAs on 16 renal transplant recipients affected by long lasting HCV infection, with moderate liver
stiffness and a well preserved renal function. Our data confirm the prolonged efficacy of DAAs in clearing viral infection and show that HCV eradication is associated with an early and persistent amelioration of self-perceived QOL.

4.1. Liver and Renal Data. All the modifications observed in liver function occurred during the 12 week treatment, and no further change was observed within the first year; similarly, hepatic stiffness greatly decreased at EOT (-33%) and remained quite stable thereafter: this huge reduction probably reflects the early improvement in liver necroinflammation induced by antiviral treatment [22].

HCV eradication did not modify mean eGFR nor proteinuria; it is noteworthy, however, that an important loss of filtrate was observed in 2 patients: the first one (combined liver/kidney transplantation) had a low baseline GFR and a high proteinuria (1.9 g/24hrs) at time of starting sofosbuvir + dasabuvir, which further increased to the nephrotic range despite the worsening of GFR (-49.5% at 1 year); the second one, conversely, presented a well preserved renal function and a proteinuria of 0.91 g/24hrs before starting sofosbuvir + ledipasvir. While, generally, our data provide confidence that DAAs do not substantially affect renal function, it remains to be elucidated whether a preexisting, consistent proteinuria may predict the worsening of renal function after treatment. Our data, however, recall those of previous studies describing an unexplained early fall of eGFR in a small number of patients [11, 13, 23].

4.2. QOL Data. Undoubtedly, the most interesting aspect of the present study is the positive effect of HCV eradication on patients’ QOL. Both questionnaires, in fact, evidenced...
interesting ameliorations in several domains, mostly relevant to the psychological sphere of our patients. At EOT, in fact, SF-36 data showed that both the well-being and the feeling of role limitation due to emotional problems were significantly better than those in Basal, and such improvements persisted after one year, associated with a healthier functioning role and a reduction in worry and emotional functioning observed with the CLDQ: taken together, all contributed to the positive perception of a beneficial modification in their QOL. Physical domains, conversely, were less affected by viral eradication; this result was in part expected, considering the long duration of HCV infection, which had probably reduced the intensity and the perception of symptoms, and the mild clinical expression of liver disease (no patient was cirrhotic).

The changes in QOL scores and, mostly, the rapidity of their improvement after DAA treatment clearly witness the heavy psychological burden that HCV infection determines in transplant recipients, who are obviously aware of the negative impact of immunosuppression on disease progression and fear the negative effects of a decompensated liver disease on the outcome of their graft; the entity of such improvement is not negligible considering that among solid organ transplant patients, kidney recipients show the lowest improvement in SF-36 after transplantation [24]. Although the questionnaires were not anonymous, but were proposed by their physician, we believe that patients did not overemphasize their feelings: all had a long follow-up in our unit and a complete confidence with their caregiver.

These data deserve attention since today QOL represents a crucial point in management of transplant recipients. In fact, traditional graft outcomes like organ survival, rejection rates, or transplant complications represent just a part of patients’ concerns, and increasing attention is devoted to QOL: patients are more and more interested in how well they feel in “real life”, considering how much the disease has modified their lives. Therefore, although QOL measurements are based on patients’ subjective sensations, they become a significant clinical measure, and patient’s perspective becomes as important as that of the clinician [25]. Unfortunately, many physicians are still reluctant to consider improvements of QOL as a main outcome of transplantation.

In general population, two different reports describe improvements in QOL after DAA treatment [19, 26]. These data, quite surprisingly, were not confirmed by Ichikawa et al. in a cohort of cirrhotic patients that showed significant ameliorations in many cirrhosis-related symptoms after treatment [27]. Probably, the life expectancy of cirrhotic patients (compared to transplant recipients) and, mostly, the degree of hepatic impairment have conditioned this result: in fact, it may require several years after relief from liver-related symptoms for an effect on QOL to become apparent [27].

Tolerability of our sofosbuvir-based regimen was excellent, as also indirectly confirmed by the improved QOL. The only serious adverse effect was an acute episode of anemia probably related to the use of ribavirin; unfortunately, the patient refused a new therapeutic trial with different drugs. The good safety profile of DAA should alert physicians to treat potential candidates as soon as possible, while on dialysis or in the transplant waiting list, to prevent further liver deterioration and improve a depressed QOL.

The main limit of our prospective study is the small sample size, due to difficulties in obtaining the drugs from our Health National System, and the inclusion of only patients with moderate liver dysfunction. Our data, however, suggest that greater improvements of QOL could be expected in patients with more pronounced symptoms and greater psychological involvement.

5. Conclusions

In conclusion, our study demonstrates that, beyond the clinical results on liver disease progression, HCV eradication by DAA determines a consistent improvement in QOL of transplant recipients. Although new studies are necessary to evaluate whether the early HCV eradication will result in improved graft outcomes, decreased recurrence of glomerulopathies, or reduced incidence of posttransplant diabetes, the possibility of improving patients’ QOL represents a further incentive to early treat all HCV-infected patients.

Abbreviations

CLDQ: Chronic Liver Disease questionnaire
DAA: Direct antiviral agents
eGFR: Estimated glomerular filtration rate
EOT: End of treatment
ESA: Erythropoiesis stimulating agents
QOL: Quality of life
SVR: Sustained virological response
TE: Transient elastography.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study was approved by the Ethical Committee of “Federico II” University (#290/15). All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.
Authors’ Contributions

Massimo Sabbatini, Nicola Caporaso, and Filomena Morisco participated in research design and in the paper writing; Ivana Capuano, Silvia Camera, Lucia Ferreri, and Laura Donnarumma participated in the performance of research; Pasquale Buonanno participated in data analysis.

References

[1] S. Baid-Agrawal, M. Pascual, D. Moradpour, R. Somasundaram, and M. Muche, “Hepatitis C virus infection and kidney transplantation in 2014: What’s new?” American Journal of Transplantation, vol. 14, no. 10, pp. 2206–2220, 2014.

[2] U. Eisenberger, H. Guberina, K. Willuweit et al., “Successful treatment of chronic hepatitis C virus infection with sofosbuvir and ledipasvir in renal transplant recipients,” Transplantation, vol. 101, no. 5, pp. 980–986, 2017.

[3] C. O. Stehman-Breen, S. Emerson, D. Gretch, and R. J. Johnson, “Risk of death among chronic dialysis patients infected with hepatitis C virus,” American Journal of Kidney Diseases, vol. 32, no. 4, pp. 629–634, 1998.

[4] R. D. Bloom, V. Rao, F. Weng, R. A. Grossman, D. Cohen, and K. C. Mage, “Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus,” Journal of the American Society of Nephrology, vol. 13, no. 5, pp. 1374–1380, 2002.

[5] M. Ladin, F. Pedraza, and D. Roth, “Hepatitis C virus infection in chronic kidney disease,” Journal of the American Society of Nephrology, vol. 27, no. 8, pp. 2238–2246, 2016.

[6] J. M. Morales and F. Fabrizi, “Hepatitis C and its impact on renal transplantation,” Nature Reviews Nephrology, vol. 11, no. 3, pp. 172–182, 2015.

[7] D. R. Scott, J. K. W. Wong, T. S. Spicer et al., “Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand,” Transplantation, vol. 90, no. 11, pp. 1165–1171, 2010.

[8] F. Fabrizi, P. Martin, V. Dixit, and P. Messa, “Meta-analysis of observational studies: Hepatitis C and survival after renal transplant,” Journal of Viral Hepatitis, vol. 21, no. 5, pp. 314–324, 2014.

[9] D. Roth, D. R. Nelson, and A. Bruchfeld, “Erratum: Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4F chronic kidney disease (the C-SURFER study): A combination phase 3 study. (Lancet (2015) 386 (1537-45)),” The Lancet, vol. 386, no. 10006, p. 1824, 2015.

[10] E. Gane, E. Lawitz, D. Pugatch et al., “Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment,” The New England Journal of Medicine, vol. 377, no. 15, pp. 1448–1455, 2017.

[11] N. Kamar, O. Marion, L. Rostaing et al., “Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection after Kidney Transplantation,” American Journal of Transplantation, vol. 16, no. 5, pp. 1474–1479, 2016.

[12] D. Sawinski, N. Kaur, A. Ajeti et al., “Successful Treatment of Hepatitis C in Renal Transplant Recipients with Direct-Acting Antiviral Agents,” American Journal of Transplantation, vol. 16, no. 5, pp. 1588–1595, 2016.

[13] M. V. Lin, M. E. Sise, M. Pavlakis et al., “Efficacy and safety of direct acting antivirals in kidney transplant recipients with chronic hepatitis C virus infection,” PLoS ONE, vol. 11, no. 7, Article ID e0158431, 2016.

[14] S. Beinhardt, R. Al Zoiray, P. Ferenci et al., “DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting,” Transplant International, vol. 29, no. 9, pp. 999–1007, 2016.

[15] S. Tanja, A. Duseja, A. De et al., “Successful treatment of chronic hepatitis C infection with directly acting antivirals in renal transplant recipients,” Nephrology, vol. 23, no. 9, pp. 876–882, 2018.

[16] M. Colombo, A. Aghemo, H. Liu et al., “Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic hepatitis C virus genotype 1 or 4 infection: A randomized trial,” Annals of Internal Medicine, vol. 166, no. 2, pp. 109–117, 2017.

[17] I. Fernández, R. Muñoz-Gómez, J. M. Pascasio et al., “Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C,” Journal of Hepatology, vol. 66, no. 4, pp. 718–723, 2017.

[18] A. L. Morales, L. Liriano-Ward, A. Tierney et al., “Ledipasvir/sofosbuvir is effective and well tolerated in postkidney transplant patients with chronic hepatitis C virus,” Clinical Transplantation, vol. 31, no. 5, p. e12941, 2017.

[19] B. M. R. Spiegel, Z. M. Younossi, R. D. Hays, D. Revicki, S. Robbins, and F. Kanwal, “Impact of hepatitis C on health related quality of life: A systematic review and quantitative assessment,” Hepatology, vol. 41, no. 4, pp. 790–800, 2005.

[20] Z. M. Younossi, G. Guyatt, M. Kiwi, N. Boparai, and D. King, “Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease,” Gut, vol. 45, no. 2, pp. 295–300, 1999.

[21] P. Rucci, G. Taliani, L. Cirrincione et al., “Validity and reliability of the Italian version of the Chronic Liver Disease Questionnaire (CLDQ-I) for the assessment of health-related quality of life,” Digestive and Liver Disease, vol. 37, no. 11, pp. 850–860, 2005.

[22] M. Persico, V. Rosato, A. Aglietti et al., “Sustained virological response by direct antiviral agents in HCV leads to an early and significant improvement of liver fibrosis,” Antiviral Therapy, vol. 23, no. 2, pp. 129–138, 2017.

[23] M. Lubetzky, S. Chun, A. Joelson et al., “Safety and Efficacy of Treatment of Hepatitis C in Kidney Transplant Recipients with Directly Acting Antiviral Agents,” Transplantation, vol. 101, no. 7, pp. 1704–1710, 2017.

[24] C. W. Pinson, I. D. Feurer, J. L. Payne, P. E. Wise, S. Shockley, and T. Speroff, “Health-related quality of life after different types of solid organ transplantation,” Annals of Surgery, vol. 234, no. 4, pp. 597–607, 2000.

[25] I. D. Feurer, R. T. Russell, and C. W. Pinson, “Incorporating quality of life and patient satisfaction measures into a transplant outcomes assessment program: Technical and practical considerations,” Progress in Transplantation, vol. 17, no. 2, pp. 121–128, 2007.

[26] Z. M. Younossi, M. Stepanova, H. L. Y. Chan et al., “Patient-reported outcomes in Asian patients with chronic hepatitis C treated with ledipasvir and sofosbuvir,” Medicine (United States), vol. 95, no. 9, Article ID e2702, 2016.

[27] T. Ichikawa, H. Miyak, S. Mima et al., “Hepatitis C virus-related symptoms, but not quality of life, were improved by treatment with direct-acting antivirals,” Hepatology Research, vol. 48, no. 3, pp. E232–E239, 2018.