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Hepatology highlights

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A Canadian national retrospective chart review comparing the long term effect of cyclosporine *vs*. tacrolimus on clinical outcomes in patients with post-liver transplantation hepatitis C virus infection

Yoshida, *et al*.[1] compared in a retrospective Canadian multicenter study cyclosporine with tacrolimus treatments regarding sustained virologic response and clinical outcomes in patients undergoing interferon-based treatment after liver transplantation due to HCV liver cirrhosis. The study cohort consisted of finally 458 patients derived from 5 transplantation centers and was confined to HCV RNA positive liver transplant recipients who received a transplant 3 to 13 years prior to the study initiation (1996-2006) in order to allow for an adequate duration of follow-up. Patients undergoing interferon-based treatment taking cyclosporine have significantly better odds (OR: 2.59, p = 0.043) of presenting a sustained viral response (67%) compared to tacrolimus (53%). This was not associated with a significant effect on post-liver transplantation clinical events including HCV-related deaths, graft loss, fibrosing cholestatic hepatitis, hepatocellular carcinoma, or graft rejection. The recommendation was given for further prospective longitudinal studies to assess the long term effect of immunosuppressive choices on the clinical outcomes in liver transplant recipients with HCV infection.

Due to inconclusive data, there is a long standing controversial issue whether cyclosporine or tacrolimus is the preferred immune suppressive treatment modality in HCV positive patients following liver transplantation, since numerous variables and endpoints are under consideration, and convincing prospective long term follow up studies are lacking.[2-4] The overall problems were also apparent in two recent studies, which again were retrospective assessments. In 2011, Irish, *et al*.[2] analyzed data received from the United Network for Organ Sharing on 8809 chronic HCV liver transplant recipients receiving either cyclosporine or tacrolimus as maintenance immunosuppression. Three-year unadjusted patient and graft survival rates were 77% and 72%, respectively, in the cyclosporine group *vs*. 80% and 75% in the tacrolimus group. In addition, propensity score-adjusted results suggest cyclosporine treated patients are at increased risk of patient death and graft failure compared to tacrolimus treated patients. In 2012, Kim, *et al*.[3] studied a total of 396 patients who underwent liver transplantation for hepatitis C virus-induced liver disease and received either cyclosporine or tacrolimus as maintenance immunosuppression. They found no significant differences between the two groups in either post-operative hepatitis C virus-RNA, histological fibrosis score, or the graft and patient survivals. Histologic hepatitis C virus recurrence-free survival, however, was significantly higher in the cyclosporine group than in the tacrolimus group (17 *vs*. 8% at 5 years). Overall, there is a need of prospective longitudinal studies with long term follow up assessments, considering also the most sensitive available tests such as the transcription–mediated amplification (TMA) assay to quantify HCV RNA levels. Of concern is the high number of HCV patients requiring liver transplantation[1-3], reflecting poor response to previously less effective treatment modalities of HCV infection and/or less effective screening methods for HCV infections in the general population in the past.

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Prediction of minimal residual viremia in HCV type 1 infected patients receiving interferon-based therapy

Knop, *et al*.[5] focused in their multicenter study from Germany on important tools to predict persistent minimal viremia during therapy by interferon plus ribavirin in patients with HCV type 1 infection. Their study cohort finally consisted of 309 treated patients who became HCV RNA negative by bDNA assay (detection limit <615 IU/mL) and provided evaluable data. In 289/309 patients (94%), on-treatment response revealed undetectable HCV RNA levels by the more sensitive TMA (transcription-mediated amplification) assay (detection limit <5.3 IU/mL). Multivariate analysis showed that initial viremia ≤ 400.000 IU/mL ($p = 0.001$), fast initial decline ($p = 0.004$), and lack of fibrosis ($p = 0.035$) were independent predictors of an accelerated on-treatment response by TMA assay in already bDNA negative patients. Most importantly, patients with bDNA negative results becoming HCV RNA undetectable by TMA assay within the following 3 weeks had a relapse rate of 21% and beyond 3 weeks a rate of 38% ($p = 0.001$).

In the past, treatment goals in patients with chronic hepatitis C infection commonly included the item of sustained virologic response, signifying an undetectable HCV RNA level at various intervals following treatment cessation. There are problems, however, when the lower limits of quantification of the assays used are either unknown[6] or declared as values up to 615 IU/mL,[7] findings not compatible with the final treatment goal of complete eradication of the hepatitis C virus. Virologic relapse in 59% of the patients even with HCV RNA levels < 5.3 IU/mL within a short time after treatment cessation illustrates the problem of minimal residual viremia in the present study,[5] calling for expanded surveillance periods after treatment discontinuation in future studies.

Vitamin D deficiency and vitamin D therapy in chronic hepatitis C

Ladero, *et al*.[8] studied in Spain the question whether the previously observed *in vitro* suppressing effect of vitamin D on HCV production can be reproduced in patients with chronic hepatitis C. Out of 108 patients, basal measurements of serum 25-hydroxy vitamin D, 25(OH) D in short, showed normal 25(OH) D levels (≥ 30 ng/mL) in 14 patients, whereas vitamin D insufficiency (20-29.9 ng/mL) and deficiency (<20 ng/mL) was present in 55 and 39 patients, respectively. Forty one patients with vitamin D insufficiency or deficiency completed oral supplementation with 25(OH) D for 5-7 weeks. No significant changes were observed when comparing baseline and end-of-therapy values of haematological and biochemical parameters as well as of HCV viral load.

Insufficiency and deficiency of 25(OH) D is a common observation both in the normal Spanish population,[9] and therefore, as expected, in the present study of Spanish patients with chronic hepatitis C,[8] but the causes for this phenomenon are poorly understood. This raises the question of an overall 25(OH) D substitution for reasons other than chronic hepatitis C. Whether this kind of substitution may be of benefit for patients with chronic hepatitis C has not yet been assessed under conditions of long term surveillance.

Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study

Wong, *et al*.[10] found in their pilot study carried out in Hong Kong that patients with histology proven nonalcoholic steatohepatitis (NASH) receiving probiotics containing various Lactobacillus species and Bifidobacterium bifidum for 6 months reduced their intrahepatic triglyceride content as measured by proton-magnetic resonance spectroscopy from 23% to 15% ($p = 0.034$). This was associated with a significant reduction of AST levels by 16%. These promising results require confirmation by larger study cohorts.

In a recent concise review on gut microbiota and nonalcoholic fatty liver disease published in Annals of Hepatology,[11] the conclusion was reached that randomized controlled clinical trials are still lacking in this particular field. On theoretical grounds, however, it was emphasized in this review that gut microbiota can play a role in the development of hepatic steatosis, necroinflammation, and fibrosis. Interference with gut microbiota through the use of probiotics as live commensal micro-organisms will modulate the intestinal microbiota, with Lactobacilli and Bifidobacteria as the most common probiotics in the market[11] used also in the present study.[10]

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