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EDITORIAL

The hepatitis C virus burden: a Dutch point of view

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The hepatitis C virus (HCV) infection is one of the leading causes of liver fibrosis and cirrhosis with more than 2.2% of the world population infected. The major routes of transmission are intravenous drug abuse and blood transfusion prior to 1992.[1] The absence of an effective HCV vaccination and the slow progression towards liver cirrhosis may pose a serious health problem in the near future. HCV can be effectively eradicated in a moderate (genotype 1, 4, 5 and 6) to substantial (genotype 2 and 3) number of patients using a combined treatment of pegylated interferon alpha 2a or 2b and ribavirin.

At the moment, newer molecules (e.g. telaprevir, boceprevir) in association with the standard of care could result in a higher HCV eradication percentage. However, in a substantial number of patients the infection is not detected before the occurrence of liver-related complications (decompensated cirrhosis, hepatocellular carcinoma) or extrahepatic manifestations (mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, lichen planus, porphyria cutanea tarda, diabetes, non-Hodgkin's lymphoma). This results in HCV being a major indication for orthotopic liver transplantation.[2]

In the absence of HCV eradication, recurrent HCV after liver transplantation ranges from minimal damage to cirrhosis developing within a few months or years in a substantial proportion of transplant recipients. Therapeutic strategies can be utilised in the pre-, peri- or post-transplantation setting. Antiviral therapy using interferon and ribavirin and modifying immune suppression are the main strategies to prevent progressive disease. Current sustained virological response rates (SVR) are approximately 28%, far below the SVR rates in the non-transplant setting.[2]

The approach to limit HCV-related complications and to lower the costs associated with the disease is multifactorial: prevent infection, identify the population at risk, estimate the seroprevalence, ameliorate treatment outcome, identify difficult/easy to treat populations and increase organ donors. In this issue of the Netherlands Journal of Medicine, two articles and two letter to the editor focus on one or more of these factors.[3-6]

The article by Slavenburg *et al.*[3] could demonstrate a low seroprevalence of HCV (0.2%) in a Dutch population. When combined with data from an earlier trial, a seroprevalence of 0.1% (95% CI 0.039 to 0.17%) was found. One can question if the collected data are from a cohort representative for the entire population. A total of 2200 persons visiting general practitioners (GP) from the urbanised region of Arnhem/Nijmegen were included. No data are included on how many more patients were invited to participate but refused, opening a possibility for a selection bias. Also, by including persons visiting a GP an overrepresentation of HCV-risk groups could be possible (e.g. a higher number of patients who had received blood transfusions or blood products prior to 1992). On the other hand, patients more concerned about their health status and therefore avoiding risk behaviour for blood-borne infections and more frequently seeking medical advice to reassure their good health status could be overrepresented. Regarding the low seroprevalence, overpresentation of high-risk groups seems unlikely. Another flaw is the age distribution (mean age of 60 years) which is not the age distribution of the entire population. Although all those objections are valid, the figures obtained were tested on robustness by comparing them with data from a previously studied population. This resulted in similar figures.

What does this seroprevalence of 0.1% (CI 0.039 to 0.17%) show us? As the authors state, this prevalence is lower than that in other European countries (e.g. Belgium has a seroprevalence of 0.9 %).[7] However, recent screening data in unselected cohorts in Belgium demonstrated a far lower prevalence (unpublished data).

As prevalence is low, this confirms that mass screening can not be cost-effective. Screening should be limited to risk groups (such as intravenous drug abusers, patients receiving blood products prior to 1992, and haemophiliacs).

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The Letter to the Editor from de Vries *et al.*[4] can help in identifying 'new' risk groups. They found that intravenous drug abuse remains the major risk behaviour for HCV (45% of the infected patients). Unknown aetiology is the second risk factor (17% of the patients) which illustrates that more epidemiological and virological research is needed to clarify the real cause(s) in this subcohort. Although the authors state that a minority of patients come from outside the Netherlands, this 'minority' is in fact four out of ten patients! The mode of transmission in this 'foreign' cohort seems similar to the entire population. In the perspective of new treatment options (e.g. more resistance and mutations are seen in genotype 1a patients *vs* genotype 1b patients treated with telaprevir), it would have been interesting to know if there was an increase/decrease of these subtypes over time. In a recent Belgian paper, a significant decrease in genotype 1b was counterbalanced by a genotype 1a increase.[8] These new Dutch epidemiological data on seroprevalence and genotype distribution can help the medical community and government in predicting the impact of this disease on the health economy of the country.

In a third contribution on HCV in this issue of the Journal, Korte *et al.*[5] present a case report describing the management of an extrahepatic HCV manifestation after liver transplantation (cryoglobulinaemia-associated glomerulonephritis).

In the seminal paper by Ojo *et al.*[9] 9% of the liver transplant patients have end-stage renal disease necessitating renal replacement therapies such as haemodialysis and kidney transplantation. In the majority of them, this is related to calcinurin inhibitory treatment.

However, patients undergoing liver transplantation for cirrhosis due to HCV infection have a greater frequency of renal insufficiency compared with patients without HCV. It is speculated that there is a higher prevalence of glomerulonephritis at the time of transplantation. In a recent American Association for the Study of Liver Diseases (AASLD) abstract,[10] it was reported that 29 of 34 patients (85%) with HCV and end-stage cirrhosis had histologically recognisable glomerular disease. In contrast, the percentage of clinical nephrotic syndrome after liver transplantation for HCV seems lower. The best way to avoid HCV-related liver and extrahepatic disease after liver transplantation is to get rid of the virus prior to transplantation. However, this is seldom achieved.

What is peculiar in this case report is the occurrence of cryoglobulinaemia associated glomerulonephritis (an immune-mediated disease) after liver transplantation (in an immunosuppressed patient). Immunosuppressive drugs used in transplantation target T cells, whereas cryoglobulinaemia associated glomerolonephritis is a B cell/antibody mediated disease. If antiviral treatment is ineffective, alternative therapies (high-dose steroids, plasmapheresis) need to be used. The effectiveness of these treatments is limited and potential side effects are severe (e.g. infections). Again, a recent AASLD abstract[11] demonstrated the risk of death to be independently associated with central nervous system involvement and the use of immunosuppressors.

Rituximab, an effective depleting monoclonal antibody for circulating CD20 bearing B lymphocytes, seemed effective in the presented case report and is possibly not linked with a higher risk of infections. However, this needs to be proven in an larger cohort.

As a conclusion, these good Dutch papers on HCV in this issue of the Journal contribute to a better understanding of HCV seroprevalence and genotype distribution in the Netherlands, and open new treatment options in the management of HCV-related extrahepatic disease post liver transplantation. However, there is still a long way to go before definitive eradication of the HCV virus is achieved.

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