Cardiovascular Involvement in Chronic Hepatitis C Virus Infections – Insight from Novel Antiviral Therapies

Wolfgang Poller1,2, Arash Haghikia1,2, Mario Kasner1, Ziya Kaya3,4, Udo Bavendiek5, Heiner Wedemeier6, Hans-Jörg Epple7, Carsten Skurk1 and Ulf Landmesser1,2

1Department of Cardiology, CC11 Charité Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Berlin, Germany; 2German Center for Cardiovascular Research (DZHK) Site Berlin, Berlin, Germany; 3German Center for Cardiovascular Research (DZHK) Site Heidelberg, Heidelberg, Germany; 4Department of Cardiology, University Hospital, Heidelberg, Germany; 5Department of Cardiology, MHH, Hannover, Germany; 6Department of Gastroenterology, MHH, Hannover, Germany; 7Department of Gastroenterology, Infectiology and Rheumatology, CC 13, Charité Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract

Whereas statistical association of hepatitis C virus (HCV) infection with cardiomyopathy is long known, establishment of a causal relationship has not been achieved so far. Patients with advanced heart failure (HF) are mostly unable to tolerate interferon (IFN)-based treatment, resulting in limited experience regarding the possible pathogenic role of HCV in this patient group. HCV infection often triggers disease in a broad spectrum of extrahepatic organs, with innate immune and autoimmune pathogenic processes involved. The fact that worldwide more than 70 million patients are chronically infected with HCV illustrates the possible clinical impact arising if cardiomyopathies were induced or aggravated by HCV, resulting in progressive HF or severe arrhythmias. A novel path has been opened to finally resolve the longstanding question of cause-effect relationship between HCV infection and cardiac dysfunction, by the recent development of IFN-free, highly efficient, and well tolerable anti-HCV regimens. The new direct-acting antiviral (DAA) agents are highly virus-specific and lack unspecific side-effects upon cardiac function which have always confounded the interpretation of IFN treatment data. The actual frequency of unexplained HF in chronic HCV infection will be determined from a planned large-scale study. Whereas such patients probably constitute a rather small fraction of all those harboring HCV, they have major clinical relevance. It is not yet known which fraction of these patients will significantly benefit from HCV eradication, but this issue will be addressed now in a prospective study.

Citation of this article: Poller W, Haghikia A, Kasner M, Kaya Z, Bavendiek U, Wedemeier H, et al. Cardiovascular involvement in chronic hepatitis C virus infections – insight from novel antiviral therapies. J Clin Transl Hepatol 2018;6(2):161–167. doi: 10.14218/JCTH.2017.00057.

Introduction

Several studies have detected an association of hepatitis C virus (HCV) infection with cardiomyopathy, but no causal relationship or mechanistic link could be established so far.1-7 Importantly, patients with advanced or pretransplant heart failure (HF) as defined by European Society of Cardiology (ESC) guidelines8 are mostly unable to tolerate interferon (IFN)-based treatment regimes, resulting in very limited experience with this patient group regarding the possible pathogenic role of HCV infections. HCV infection often triggers disease in a broad spectrum of extrahepatic organs,9-11 with innate immune and autoimmune pathogenic processes being involved.12-16 and involvement of the myocardium in HCV-triggered autoimmunity would therefore not come as a surprise. There is no need to assume that HCV directly infects the myocardium, or that HCV impairs the function of a healthy heart and thus constitutes an independent cause of cardiomyopathy and HF. For HCV to have relevance for cardiovascular medicine it would already be sufficient that it indirectly disrupts cardiac function via an immune mechanism, and does so particularly in already injured hearts. In all cases, HCV elimination could result in functional improvement.

The fact that worldwide more than 70 million patients are chronically infected with HCV illustrates the possible clinical impact arising if cardiomyopathies were induced or aggravated by HCV.14,17 If progressive HF or severe arrhythmias were induced in even a small fraction of all HCV-positive patients, this would still constitute a grave clinical problem. For this reason, it is most welcome that the long-standing hypothesis of cause-effect relationship between HCV infection and cardiac dysfunction may be conclusively tested now, enabled by the recent introduction of highly efficient and virus-specific direct-acting antiviral (DAA)-based anti-HCV regimens.18-23 Cardiac functional effects of DAA-based HCV

Keywords: Autoimmunity; Cardiovascular immunity; Cardiomyopathies; Hepatitis C virus; Antiviral therapies.

Abbreviations: Adv, adenovirus; B19V, parvovirus B19; CAR, coxsackievirus-adenovirus-receptor; CI, confidence interval; CLDN1, claudin1; CRP, cardiomyopathy; CVB3, Coxsackievirus B3; CVD, cardiovascular disease; DAA, direct-acting antiviral; DAP, decay accelerating factor; EBV, Epstein-Barr virus; EGFR, EGF receptor; EMRs, endothelial myocardial biopsies; EphA2, ephidine A2; ESC, European Society of Cardiology; HCV, hepatitis C virus; HF, heart failure; HHV6, human herpes virus 6; HTA, host targeting agents; HTX, heart transplantation; IFN, interferon; IRES, internal ribosome entry site; LDL-R, LDL receptor; NS, nonstructural protein; OCLN, occludin; OR, odds ratio; PBMC, peripheral blood mononuclear cell; RdRp, RNA-dependent RNA polymerase; SR-B1, scavenger receptor B1.

Received: 22 August 2017; Revised: 6 December 2017; Accepted: 23 December 2017.

*Correspondence to: Wolfgang Poller, Department of Cardiology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Hindenburgdamm 30, Berlin 12200, Germany. Tel: +49-30-450-513765, Fax: +49-30-450-513984, E-mail: wolfgang.poller@charité.de

Journal of Clinical and Translational Hepatology 2018 vol. 6 | 161–167

Copyright: © 2018 Authors. This article has been published under the terms of Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided: "This article has been published in Journal of Clinical and Translational Hepatology at DOI: 10.14218/JCTH.2017.00057 and can also be viewed on the Journal's website at http://www.jcthnet.com".
HCV virology and immunology and possible cardiac pathomechanisms

After the discovery of HCV and generation of infectious molecular cDNA clones in 1997,29,30 HCV was classified as prototype *Hepacivirus* into the *Flaviviridae* family. HCV constitutes a diversified group of viruses classified into seven genotypes and multiple subtypes, circulating in those infected as continuously evolving quasispecies.17,31,32 The same phenomenon, which is based on lack of proof-reading activity of the virus-encoded RdRp, is also observed for CVB3,31 the prototype virus causing myocarditis and often resulting in dilated cardiomyopathy.34–36 For both HCV and CVB3, continuous diversification of virus genome sequences has been documented. HCV resembles CVB3 in another important molecular aspect. Both have positive-sense single-stranded RNA genomes which in the host cells serve directly as messenger RNA (Fig. 1B), and in association with modified cell membranes as template for replication through negative-strand full-length intermediates.37,38 Both HCV and CVB3 employ internal ribosome entry site (IRES)-mediated translation and polyprotein processing of the long primary virus-encoded mRNA, and both use a particular type of polymerases designated as RdRp, which are important drug targets (Fig. 1B).

The molecular mechanisms of HCV and CVB3 replication therefore display important similarities, whereas tissue tropism and details of replication differ greatly. Cell surface receptors known to be involved in HCV and CVB3 attachment and internalization are depicted in Fig. 1A. With regard to tissue tropism, it should be noted that this need not be comprehensively determined by the normal receptor complement of target cells, i.e. CVB3 always being targeted to cardiomyocytes or HCV to hepatocytes only. Instead, breakdown of endothelial barriers or alterations of cell surface receptor expression induced by any disease39–43 may lead to retargeting of a virus to organs and targets cells normally inaccessible to this specific virus. Thus, one report described the presence of HCV genomes in the myocardium4 by direct analysis of EMBs.

Interferons as primarily host-targeting and rather unspecific therapeutic agents were used for virus suppression or elimination in HCV as well as CVB3 infections. The efficacy of IFN-α was found to be high regarding virus elimination in CVB3 cardiomyopathy patients, resulting in less urgent clinical need for the development of CVB3-specific DAAAs.44,45 This is in sharp contrast to HCV elimination which could not be reached by use of IFN-based regimens, resulting in a high clinical need
for DAAs against HCV. Another, clinically and economically important aspect of the far more intense research into anti-HCV DAAs as compared to anti-CVB3 drugs is the fact that CVB3 cardiomyopathy is a rather rare disease, whereas HCV infections are among the most frequent and important viral diseases worldwide. Millions of patients are newly infected with HCV each year, chronicity rate is high, and over 70 million individuals are known to be infected.

According to current knowledge HCV replicates primarily, if not exclusively, in the patients’ hepatocytes, and its replication is strongly dependent on the liver-specific micro-RNA-122 which led to the development of a fundamentally novel anti-HCV therapeutic strategy based on a anti-miR-122 antagonist (miravirsen). A number of other host molecules critical for HCV entry and replication were identified, revealing important targets for the development of host targeting agents (HTAs). Although the use of miravirsen in patients with chronic HCV genotype 1 infection resulted in prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance, this path is no
longer followed and has been replaced by DAAs with their significantly higher efficacy and eradication potential. Likewise, none of the several anti-receptor strategies to block attachment and/or internalization of HCV or CVB3 has so far proceeded to the stage of clinical evaluation. Whereas these studies have addressed host-related molecular mechanisms, other investigations of outstanding importance have addressed the structures and functions of essential HCV-encoded proteins, in particular three of those classified as nonstructural (NS). The identification and characterization of these structures and functions has been the subject of several studies, including transcriptome profiling, immunophenotyping, and assessment of viral load. Additionally, assessment of cardiac function and anti-viral therapy have been included in the study to determine the impact of HCV eradication upon the course of myocardial diseases.

**Figure 2. Study to determine the impact of HCV eradication upon the course of myocardial diseases.** The actual frequency of the combination of cardiomyopathy with chronic HCV infection is currently unknown. This study shall recruit a large number of HCV patients with myocardial disease who are in need and eligible for state-of-the-art HCV eradication. Cardiological follow-up will reveal to what extent, and in which fraction of these patients, HCV eradication does improve cardiac function. For HCV to reach cardiovascular therapeutic relevance it would be sufficient that it indirectly disturbs cardiac function via immune mechanism, even if it does so only or particularly in already pre-injured hearts. Therefore, the study shall not only include patients with inexplicable left or right heart dysfunction or morphology, but also patients with nonvalvular and nonischemic cardiomyopathies, and pulmonary hypertension and/or right heart dysfunction of any cause. In these cases, HCV infection may adversely affect the “natural course” of the cardiac disease. The study is primarily based on noninvasive assessment (serial echocardiographies, HF biomarkers) to ascertain the frequency of combination of cardiomyopathy with HCV infection. In a subgroup of patients with advanced cardiac dysfunction and/or on extensive morphological anomalies, right/left ventricular EMBs are to be performed in accordance with ESC guidelines. Patients are classified as IMPs if LVEF increases by 10 absolute percent units or if NYHA improves by one class. Patients are classified as NIMPs if they show at the follow-up visit any of the parameters such as an LVEF <35 %, failure to improve LVEF by 10 absolute units, remaining at a NYHA functional class of III/IV or obtaining heart transplantation/ventricular assist device or if patients die. Full recovery is defined as reaching an LVEF of >55 % and NYHA class I. Abbreviations: ESC, European Society of Cardiology; EMBs, endomyocardial biopsies; HCV, hepatitis C virus; HF, heart failure; IMPs, improvers; LVEF, left ventricular ejection fraction; NIMPs, nonimprovers.

**Exclusion criteria:**
- Coronary heart disease/ischemic cardiomyopathy
- Valvular cardiomyopathy
- Hypertensive cardiomyopathy

**Cardiac evaluation of patients with chronic hepatitis C virus infection**

**Assessment of viral load**
- Immunophenotyping
- Transcriptome profiling

**Evaluation of cardiac function**
- Assessment of viral load

**HCV-positive cardiomyopathy**

**Anti-viral therapy + heart failure therapy**

**Full-recovery**

**Improver**

**Non-improver**

**Evaluation of prognostic determinants**

**Abbreviations:** ESC, European Society of Cardiology; EMBs, endomyocardial biopsies; HCV, hepatitis C virus; HF, heart failure; IMPs, improvers; LVEF, left ventricular ejection fraction; NIMPs, nonimprovers.
HCV-encoded proteins and their functional units enabled the development of highly effective DAAAs against the NS3 protease, NSSA and the NS5B polymerase of HCV. As already discussed above, IFN-free regimens based on these DAAAs are not only far more efficient than IFN regarding HCV elimination, but they also have far less side effects. In combination, these DAA agents enabled IFN-free therapy with cure rates over 90% among patients with chronic HCV infection. Nevertheless, viral resistance represents a problem not yet fully solved.

**Outlook from the cardiovascular perspective**

**Frequency of cardiac dysfunction in chronic HCV infection**

One may safely assume that screening of retrospective series of HCV-positive patients for evidence of unexplained myocardial disease will only detect those with grave myocardial disease. Otherwise either the myocardial disturbance (e.g., isolated diastolic dysfunction) will go undetected, or in cardiological patients there are no data regarding possible HCV infection since there was no clinical hint for liver disease, and hence no apparent need for virus-specific diagnostics. The actual frequency of the combination of cardiomyopathy with chronic HCV infection therefore shall be determined in a prospective study (Fig. 2).

**Cardiovascular therapeutic relevance of HCV elimination**

In order to proceed beyond the question of frequency to possible cardiovascular therapeutic impact, this study has to recruit a sufficiently large number of HCV patients with cardiac dysfunction who are in need and eligible for state-of-the-art HCV eradication. Careful cardiological follow-up will then reveal to what extent, and in which fraction of these patients, HCV eradication does in fact improve cardiac function. For HCV to reach cardiovascular therapeutic relevance it would suffice that it indirectly disturbs myocardial function via immune mechanism, even if it does so only or particularly in already pre-injured hearts. There is no need to assume that HCV directly infects the myocardium, or impairs the function of a healthy heart, thus constituting an independent cause of cardiomyopathy and HF. Therefore, the study shall not only include patients with inexplicable left or right heart dysfunction or morphology, but also patients with nonvalvular and nonischemic cardiomyopathies, and with pulmonary hypertension and/or right heart dysfunction of any cause. In these cases, the HCV infection might adversely affect the “natural course” of the cardiac disease.

**Persistent immune system anomalies despite successful HCV elimination**

The study is primarily based on noninvasive functional assessment of patients (serial echocardiography, HF biomarkers) which allows to ascertain the frequency of the combination of cardiomyopathy with HCV infection, and to address the question of cardiovascular therapeutic impact. In a subgroup of patients with advanced cardiac dysfunction and/or extensive morphological anomalies (e.g., massive left/right ventricular hypertrophy), right/left ventricular EMBs are to be performed in accordance with ESC guidelines EMBS, providing molecular virological data, immunohistological data and immune-related gene expression profiles to identify and characterize inflammation, and histology to detect storage diseases. In addition, cardiac autoantibody arrays will be conducted immediately before and 6 months after HCV elimination.

Several sets of data suggest that myocardial dysfunction and pathogenesis in chronically-infected HCV patients are immune-mediated. First, several studies have documented that autoantibodies to myocardial proteins including troponin and others may aggravate cardiac dysfunction, and have prognostic relevance. Virus infections induce an innate immune response not only when active viral replication takes place, but also in latent infections with even minimal viral synthesis of immunogenic nucleic acids or proteins. In addition to this primordial innate immune activation, there may be virus-triggered autoantibody formation by molecular mimicry or other mechanisms. Second, it has been shown that DAA-induced HCV clearance does not completely restore the altered cytokine and chemokine milieu from the above immunohistological and serological characterization of the patients before and after virus elimination one may expect further insights into HCV-associated myocardial pathogenesis.

**Conflict of interest**

The authors have no conflict of interests related to this publication.

**Author contributions**

WP drafted the manuscript which was discussed and improved by all authors. The prospective HCV study described was derived from discussions among the authors all of whom will be involved in this project.

**References**

[1] Matsumori A. Hepatitis C virus infection and cardiomyopathies. Circ Res 2005;96:144–147. doi: 10.1161/01.RES.0000156077.54903.67.
[2] Boyella V, Onyebueke I, Farrar J, Graham-Hill S, EI Younis C, Bergasa NV. Prevalence of hepatitis C virus infection in patients with cardiomyopathy. Ann Hepatol 2009;8:113–115.
[3] Omura T, Yoshiyama M, Hayashi T, Nishiguchi S, Kaito M, Horishe S, et al. Core protein of hepatitis C virus induces cardiomyopathy. Circ Res 2005;96: 148–150. doi: 10.1161/01.RES.0000154263.70223.11.
[4] Okabe M, Fukuda K, Arakawa K, Kikuchi M. Chronic variant of myocarditis associated with hepatitis C virus infection. Circulation 1997;96:22–24. doi: 10.1161/01.CIR.96.1.22.
[5] Illyas SZ, Tabassum R, Hamed H, Rehman SU, Qadri I. Hepatitis C virus-associated extrahepatic manifestations in lung and heart and antiviral therapy-related cardiopulmonary toxicity. Viral Immunol 2017;30:633–641. doi: 10.1089/vim.2017.0009.
[6] Demir C, Demir M. Effect of hepatitis C virus infection on the right ventricular functions, pulmonary artery pressure and pulmonary vascular resistance. Int J Clin Exp Med 2014;7:2314–2318.
[7] Kati V, Fekete I, Skevofillis X, Allgeier C, Tousoulis D, Stefanadis C, et al. Cardiovascular disease and hepatitis C virus infection: an irrelevant statement or a hot relationship? Cardiol Rev 2015;23:11–17. doi: 10.1097/CRD. 0000000000000331.
[8] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975. doi: 10.1002/ejhf.592.
[9] Voulgaris T, Sevastianos VA. Atherosclerosis as extrahepatic manifestation of chronic infection with hepatitis C virus. Hepat Res Treat 2016;2016:7629318. doi: 10.1155/2016/7629318.
[10] Petta S, Maida D, Macaluso FS, Barbara M, Licata A, Craxi A, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality:
Hepatitis C virus and cardiovascular disease

Pinkert S, Westermann D, Wang X, Klingel K, Dörner A, Savvatis K, Fechner H, Sipo I, Westermann D, Pinkert S, Wang X, Suckau L, Fechner H, Pinkert S, Wang X, Sipo I, Suckau L, Kurreck J, Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the treatment of cardiovascular disease.

Eckstein A, Grössl T, Geisler A, Wang X, Pinkert S, Pozzuto T, Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Tschöpe C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL, et al. High prevalence of cardiac parvovirus B19 infection in patients with dilated left ventricular diastolic dysfunction.

Kühl U, Lassner D, Dorner A, Rohde M, Escher F, Seeberg B, Lassner D, Stroux A, Gross UM, Seeberg B, Noutsias M, et al. Prevalence of erythrovirus genotypes in the myocardium of patients with dilated cardiomyopathy.

Kühl U, Lassner D, Ormerod A, Rohde M, Escher F, Seeberg B, et al. A distinct subgroup of dilated cardiomyopathy patients characterized by transcriptionally active cardiac tropic erythrovirus and altered cardiac gene expression.

Escher F, Kühl U, Gross U, Westermann D, Poller W, Tschöpe C, et al. Aggravation of left ventricular dysfunction in patients with biopsy-proven cardiac human herpesvirus A and B infection.

Jopling CL, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA.

Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. N Engl J Med 2013;368:1685–1694. doi:10.1056/NEJMoa1209026.

Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 2017;16:203–222. doi:10.1038/nrd.2016.246.

Fechner H, Pinkert S, Wang X, Sipo I, Suckau L, Kurreck J, et al. Coxsackievirus B3 and adenovirus infections of cardiac cells are efficiently inhibited by vector-mediated RNA interference targeting their common receptor.

Fechner H, Sipo I, Westermann D, Pinkert S, Wang X, Suckau L, et al. Cardiac-targeted RNA interference mediated by an AAV9 vector improves cardiac function in coxsackievirus B3 cardiomyopathy.

Pinkert S, Westermann D, Wang X, Klingel K, Dörner A, Savvatis K, et al. Prevention of cardiac dysfunction in acute coxsackievirus B3 cardiomyopathy by inducible expression of a soluble coxsackievirus-adenoceptor receptor.

Werk D, Pinkert S, Heim A, Zeichhardt H, Grunert HP, Poller W, et al. Combination of soluble coxsackievirus-adenoceptor and anti-coxsackievirus siRNAs exerts synergistic antiviral activity against coxsackievirus B3. Antiviral Res 2009;83:298–306. doi:10.1016/j.antiviral.2009.07.002.

Eckstein A, Grössl T, Geisler A, Wang X, Pinkert S, Pozzuto T, et al. Inhibition of adenovirus infections by siRNA-mediated silencing of early and late adenoviral gene functions. Antiviral Res 2010;88:86–94. doi:10.1016/j.antivir.2010.08.002.

Stein EA, Pinkert S, Becher PM, Geisler A, Zeichhardt H, Klopfließ R, et al. Combination of RNA interference and virus receptor trap exerts additive antiviral activity in coxsackievirus B3-induced cardiomyitis in mice. J Infect Dis 2015;211:613–622. doi:10.1093/infdis/jiu506.

Escher F, Lassner D, Kühl U, Gross U, Westermann D, Poller W, et al. Analysis of endomyocardial biopsies in suspected myocarditis—diagnostic value of left versus right ventricular biopsy. Int J Cardiol 2014;177:76–78. doi:10.1016/j.ijcard.2014.07.011.

Escher F, Kühl U, Lassner D, Stroux A, Westermann D, Skurk C, et al. Presence of perforin in endomyocardial biopsies of patients with inflammatory cardiomyopathy predicts poor outcome. Eur J Heart Fail 2014;16:1066–1072. doi:10.1002/ejhf.148.

Escher F, Kühl U, Lassner D, Stroux A, Gross U, Westermann D, et al. High perforin-positive cardiac cell infiltration and male sex predict adverse long-term mortality in patients with inflammatory cardiomyopathy. J Am Heart Assoc 2017;6:e005352. doi:10.1161/JAHA.116.005352.

Müller AM, Bockstahler M, Hristov G, Weiss C, Fischer A, Korkmaz-Iöz S, et al. Identification of novel antigens contributing to autoimmunity in cardiovascular diseases. Clin Immunol 2016;173:64–76. doi:10.1016/j.clim.2016.09.003.

Kaya Z, Göser S, Buss SJ, Leuschner F, Ott R, Li J, et al. Identification of cardiac troponin I sequence motifs leading to heart failure by induction of myocardial inflammation and fibrosis. Circulation 2008;118:2063–2072. doi:10.1161/CIRCULATIONAHA.108.788711.

Göser S, Andrássy M, Buss SJ, Leuschner F, Volz CH, Ott R, et al. Cardiac troponin I but not cardiac troponin T induces severe autoimmune inflammation in the myocardium. Circulation 2006;114:1693–1702. doi:10.1161/CIRCULATIONAHA.106.635664.

Leuschner F, Li J, Göser S, Reinhardt L, Ott R, Bride R, et al. Absence of auto-antibodies against cardiac troponin I predicts improvement of left ventricular function after acute myocardial infarction. Eur Heart J 2008;29:1949–1955. doi:10.1093/eurheartj/ehn268.

Doesch AO, Mueller S, Nelles M, Konstandin M, Celik S, Frankenstein L, et al. Impact of troponin I-autoantibodies in chronic dilated and ischemic cardiomyopathy. Basic Res Cardiol 2011;106:25–35. doi:10.1007/s00395-010-0126-z.

Doesch AO, Konstandin M, Celik S, Kristen A, Frankenstein L, Hardt S, et al. Effects of protein A immunoadsorption in patients with advanced chronic dilated cardiomyopathy. J Clin Apher 2009;24:141–149. doi:10.1002/jca.2024.

Goubau D, Deddouche S, Reis e Sousa C. Cytosolic sensing of viruses. Immunity 2013;38:855–869. doi:10.1016/j.immuni.2013.05.007.

Yan N, Chen Z. Intrinsic antiviral immunity. Nat Immunol 2012;13:214–222. doi:10.1038/ni.2229.

Hengst J, Falk CS, Schlalphoff V, Detending K, Manns MP, Cornberg M, et al. Direct-acting antiviral-induced hepatitis C virus clearance does not completely restore the altered cytokine and chemokine milieu in patients with chronic hepatitis C. J Infect Dis 2016;214:1955–1965. doi:10.1093/infdis/jiw457.

Hengst J, Strunz B, Detending K, Ljunggren HG, Leenansyah E, Manns MP, et al. Nonreversible MAIT cell dysfunction in chronic hepatitis C virus infection despite successful interferon-free therapy. Eur J Immunol 2016;46:2204–2210. doi:10.1002/eji.201646447.

Owusu Sekyere S, Suneetha PV, Hardtke S, Falk CS, Hengst J, Manns MP, et al. Type I interferon elevates co-regulatory receptor expression on CMV- and EBV-specific CD8 T cells in chronic hepatitis C. Front Immunol 2015;6:270. doi:10.3389/fimmu.2015.00270.