HHS Public Access

Author manuscript

Clin Liver Dis (Hoboken). Author manuscript; available in PMC 2018 August 16.

Published in final edited form as:

Clin Liver Dis (Hoboken). 2018 May ; 11(5): 115–118. doi:10.1002/cld.705.

Treatment of the Extrahepatic Manifestations of Chronic Hepatitis C infection

Karn Wijarnpreecha[1,*], **Wisit Cheungpasitporn**[2], **Surakit Pungpapong**[3], and **Kiran R. Nakkala**[4]

[1]Department of Internal Medicine, Bassett Medical Center, Cooperstown, NY, USA

[2]Division of Nephrology, Department of Internal Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

[3]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, Jacksonville, Florida, USA

[4]Division of Gastroenterology, Cape Fear Center for Digestive Diseases, Fayetteville, NC, USA

Nearly 75 percent of patients with hepatitis C virus (HCV) infection develop some type of extrahepatic manifestations (EHM), including immune-related and inflammatory-related EHM as shown in Table 1 [1]. Treatment of the EHMs of HCV may be directed towards eradicating HCV or controlling vasculitis. Successful eradication of HCV in the first approach is associated with resolution of complications of cryoglobulinemia, improved sensitivity to insulin, reduced incidence of diabetes and stroke, and improved fatigue and cognitive functioning [2]. The second approach aims to reduce vascular inflammation by suppressing the clonal expansion of B-lymphocytes which produce cryoglobulins, more general anti-inflammation therapies, or by removal of circulating cryoglobulins by means of plasmapheresis.

A Historical Look Back.

The history of the use of antiviral treatment to ameliorate EHMs follows in parallel with the evolution of HCV therapy. Initial reports used interferon-based regimens, wherein improvement was seen even when though sustained clearance of the virus was infrequent. Just as direct-acting antivirals (DAA) have eclipsed interferon and ribavirin in the treatment of HCV in general, DAA have been brought to bear in EHMs. As we shall see, these agents have simplified some of the choices for the physician treating new onset EHMs of HCV. Furthermore, the efficacy and tolerability of the current DAAs have made much of the earlier literature on treating EMHs redundant, and nowadays there is no indication to use interferon-based therapy of patients with EMHs of HCV.

[*]Corresponding author; Karn Wijarnpreecha, MD, Address: One Atwell Road, Cooperstown, NY, USA, 13326, Phone: 607-547-4805, Fax: 604-547-6612, dr.karn.wi@gmail.com.

Authors' contributions: Wijarnpreecha K, Cheungpasitporn W contributed to conception and manuscript writing; Pungpapong S, Nakkala K revised the article; all authors approved the final revision.

Conflict of interest statement for all authors: We do not have any financial or non-financial potential conflicts of interest.

Treatment of HCV-associated EHMs in 2018

When we look at the landscape in 2018, we find that the guidelines of the AASLD/IDSA, and of EASL are in agreement that all patients with HCV infection should be treated with effective antiviral therapy [3, 4]. Table 2 categorizes HCV-associated EHMs according to severity [5]. Treatment of patients with mild to moderate HCV-associated EHMs is important since the first-line treatment of HCV-associated EHMs of mild/moderate severity is always initiation of DAA therapy. Patients with severe or life-threatening EHMs of HCV should also receive the most appropriate DAAs.

1. Immune-related EHM

1.1 Mixed Cryoglobulinemic Syndrome

Current evidence supports the use of antiviral therapy in HCV-infected patients with EHM, especially in MCS [3, 4]. The most recent study shows the benefit of HCV treatment in those with MCS [6]. Rituximab has been increasingly used to treat HCV-induced cryoglobulinemic vasculitis [1]. Treatment of aggressive lymphoma or EHM with rituximab should require an individualized assessment of the benefits and risks [5]. A summary of the current evidence shows that interferon (IFN)-based regimens have a higher complete clinical response, but lower SVR rates than IFN-free regimens [5]. However, the high heterogeneity in patient characteristics and differences in DAA regimens used in each study could limit the strength of this conclusion. It is apparent that DAA regimens should be the current choice to treat HCV-infected patients with MCS because IFN-based regimens can increase the risk of developing autoimmune diseases, lower SVR rates, and other adverse effects [5].

1.2 B-cell Non-Hodgkin Lymphomas

The studies demonstrated 80 percent of HCV-infected patients with non-Hodgkin lymphoma (NHL) and other lymphoproliferative disorders achieved complete or partial response and improved overall survival following HCV treatment with IFN-based regimens [7]. EASL guidelines strongly recommended assessing the severity of liver disease prior to HCV therapy [3]. Noninvasive fibrosis assessment methods such as transient elastrography, and/or biomarkers of fibrosis can be used instead of liver biopsy. The decision to initiate antiviral therapies will include the assessment of the severity of presentation. Future study will provide additional data to aid in this decision process. Most of the current experience using DAA regimens came from case reports except the most recent study. That study reported that the DAA regimen achieved similar remission rates in NHL with a higher SVR rate when compared to IFN-based regimens, although 2 patients developed highly aggressive lymphoma one month after sofosbuvir therapy [8]. Further studies evaluating the efficacy and safety of DAA regimens in NHL are still required. Due to a lack of solid evidence of IFN-free DAA regimens, the IFN-based regimen can be considered in patients with NHL. Recent evidence shows that patients with DAA regimens also significantly improved in clinical outcomes, higher SVR rates, and prolonged disease-free survival after NHL remission [9].

2. Inflammatory-related EHM

2.1 Non-specific Symptoms and Quality of Life

Many HCV-infected patients experience general symptoms such as chronic pain, fatigue, and fibromyalgia which can significantly impact quality of life. IFN-based regimens are significantly associated with more adverse effects such as fatigue and depression compared to DAA regimens [5]. A study showed the benefit of DAA therapies on health-related quality of life, defined as improved physical status and work productivity [10]. Achievement of SVR following the DAA treatment for 12 weeks is associated with improvement in health-related quality of life and cognitive function including memory, visuospatial memory, and learning.

Future Perspective of HCV Treatment—DAA regimens have been approved by the FDA and have been available since 2013. To date no studies report the adverse effects of these regimens on EHM in HCV-infected patients. We reviewed well-established data of IFN-based regimens and the limited data of the newer DAA regimens to compare the efficacy and adverse effects between these regimens. There are many gaps in knowledge of the efficacy of the DAA therapies and adverse effects on particular EHM in HCV-infected patients. Further studies will be required to elucidate these outcomes.

Conclusion

Current evidence clearly shows that DAA regimens have higher efficacy and fewer side effects when compared to the old IFN-based regimens. Treatment with DAA regimens should be the first-line regimen for all HCV-infected patients with EHM [5]. The selection of which DAA is best for a particular patient should be based on the current guidelines, and we recommend the AASLD/IDSA website, which has managed to keep abreast of a fast-changing field [4]. Finally, IFN-based regimens or first-generation DAA, neither of which is in use in developed countries, are still utilized in several developing countries. Guidance to navigate the system to increase access to DAA therapy for patients in developing countries is warranted.

Acknowledgement

We thank Matthew Roslund for helping us to proofread the manuscript.

Funding: None

References

1. Cacoub P , Comarmond C , Domont F , Savey L , Saadoun D . Cryoglobulinemia Vasculitis. The American journal of medicine. 2015;128(9):950–5. [PubMed: 25837517]
2. Negro F , Forton D , Craxi A , Sulkowski MS , Feld JJ , Manns MP . Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology. 2015;149(6):1345–60. [PubMed: 26319013]
3. European Association for Study of L. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. Journal of hepatology. 2014;60(2):392–420. [PubMed: 24331294]
4. Panel AIHG . Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62(3):932–54. [PubMed: 26111063]

5. Ramos-Casals M , Zignego AL , Ferri C , Brito-Zeron P , Retamozo S , Casato M , et al. Evidence-based recommendations on the management of extrahepatic manifestations of chronic hepatitis C virus infection. Journal of hepatology. 2017;66(6):1282–99. [PubMed: 28219772]

6. Saadoun D , Pol S , Ferfar Y , Alric L , Hezode C , Si Ahmed SN , et al. Efficacy and Safety of Sofosbuvir Plus Daclatasvir for Treatment of HCV-Associated Cryoglobulinemia Vasculitis. Gastroenterology. 2017;153(1):49–52 e5. [PubMed: 28288791]

7. Gisbert JP , Garcia-Buey L , Pajares JM , Moreno-Otero R . Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. Alimentary pharmacology & therapeutics. 2005;21(6):653–62. [PubMed: 15771751]

8. Arcaini L , Besson C , Frigeni M , Fontaine H , Goldaniga M , Casato M , et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood. 2016;128(21):2527–32. [PubMed: 27605512]

9. Persico M , Aglitti A , Caruso R , De Renzo A , Selleri C , Califano C , et al. Efficacy and safety of new direct antiviral agents in hepatitis C virus-infected patients with diffuse large B-cell non-Hodgkin's lymphoma. Hepatology. 2018;67(1):48–55. [PubMed: 28714143]

10. Younossi ZM , Stepanova M , Henry L , Nader F , Hunt S . An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens. The American journal of gastroenterology. 2016;111(6):808–16. [PubMed: 27021197]

Table 1

Extrahepatic Manifestations of Hepatitis C Viral Infection

Mixed cryoglobulinemic syndrome (MCS)
Membrano-proliferative glomerulonephritis,
Leukocytoclastic vasculitis
Cerebral vasculitis/neuropathy
Thyroiditis
Digital ischemia
B-cell Non-Hodgkin Lymphoma
Diabetes mellitus
Porphyria cutanea tarda
Lichen Planus
Mooren Ulcer

Rheumatic/autoimmune systemic diseases (i.e., Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, hemolytic anemia/thrombocytopenia)

Coronary artery disease/stroke.

General symptoms: Fatigue; cognitive slowing, Arthralgia/arthritis

Table 2

HCV-associated EHMs classified according to severity

Mild/moderate manifestations
Purpura
Single, sporadic skin ulcers
Arthralgia/arthritis/ Non-inflammatory musculoskeletal pain
General features (malaise, fatigue, cognitive slowing)
Mild/moderate neuropathies (sensory)
Severe manifestations
Recurrent, multiple, non-healing cutaneous ulcers/digital ischemia
Severe neuropathy (motor or sensory-motor)
Glomerulonephritis with/without renal failure/nephrotic syndrome
Interstitial lung disease
Vasculitic gastrointestinal involvement (non-necrotizing)
Severe autoimmune cytopenias
Life-threatening manifestations
Rapidly progressive glomerulonephritis
CNS involvement
Acute intestinal necrotizing vasculitis
Alveolar hemorrhage
Coronary artery involvement (excluding other etiologies)