Turk J Gastroenterol *2017; 28(Suppl 2): S84-S89*

Diagnosis, management and treatment of hepatitis delta virus infection: Turkey 2017 Clinical Practice Guidelines

Panel Chairmen: Cihan Yurdaydın, Fehmi Tabak

Coordinators: Sabahattin Kaymakoğlu and Fehmi Tabak

Panel Members (alphabetically): Mesut Akarsu, Esra G. Akıncı, Hikmet Akkız, Canan Alkım, Ayhan H. Çekin, Nefise Ö. Çuvalcı, Kadir Demir, Bülent Değertekin, İlyas Dökmetaş, Galip Ersöz, Kenan Hizel, Fatma Ö. Kandemir, Yusuf Önlen, Abdullah Sonsuz, Ebubekir Şenateş, Selma Tosun, Nurdan Tözün, Ramazan Idilman, and Viral Hepatitis Guidelines Study Group

Turkish Association for the Study of the Liver, İstanbul, Turkey
Viral Hepatitis Society, Ankara, Turkey

Cite this article as: Yurdaydın C, Tabak F, Idilman R; Viral Hepatitis Guidelines Study Group. Diagnosis, management and treatment of hepatitis delta virus infection: Turkey 2017 Clinical Practice Guidelines. Turk J Gastroenterol 2017; 28(Suppl 2); S84-S89.

DIAGNOSIS IN HEPATITIS D VIRUS (DELTA) INFECTIONS

Hepatitis D virus (HDV) infection can appear in the form of a co-infection of HDV with hepatitis B virus (HBV) or may develop as a superinfection with HDV of hepatitis B surface antigen (HBsAg)-positive individuals (1). Co-infections and super infections differ from each other in terms of their long-term effects. Clinically acute HDV infection presents with a picture similar to those of other hepatotrophic viruses-related hepatitis. Fatigue, poor appetite, nausea, vomiting and jaundice are the main complaints. In co-infections serum amino transferases levels are usually elevated twice, 2-5 weeks apart from each other. The first elevation is generally related with HBV infection, whereas the second is associated with HDV infection. The acute clinical picture usually disappears by itself within 2-10 weeks (1-3). The risk of development of fulminant hepatitis during a HBV and HDV co-infection is higher than that caused by HBV mono-infection. The risk of developing HDV-induced fulminant hepatitis has been clearly shown in 1980s (1,2). Today, fulminant delta hepatitis is not seen as frequently as it has been seen in the past (3). This may be explained that the frequency and turnover of HDV in the population has decreased (3,4). During co-infection, HDV can suppress the replication of HBV and HBsAg may be lost. In this instance, the diagnosis is established the presence of antibody to hepatitis B core antigen (anti-HBc) immunoglobulin M (IgM) antibody positivity (Table 1). The risk of chronicity in co-infected patients is not different than that of patients with acute HBV infection (3-5).

Hepatitis D virus superinfection in HBsAg-positive individuals is also characterized by hepatitis exacerbation. HDV superinfection results in chronic HDV infection in 70-90% of the cases. In a limited number of cases, HDV superinfection may lead to clearance either HDV or both HDV and HBV infections. Chronic delta hepatitis (CDH) generally has a more severe course compared to chronic hepatitis B (CHB) (5-7). In addition, cirrhosis and liver failure develop more rapidly in CDH. The clinical presentations of CDH vary from a mild-course of disease to acute on chronic liver failure as a result of HDV-related immune-mediated damage. Patients often reported a history of an acute hepatitis attack, which is probably associated to the period where HDV superinfection develops. There is no specific clinical finding for CDH. Patients commonly have fatigue, poor appetite, muscle-joint pain and right hypochondriac pain. In physical examination, most of the cases might have findings of chronic hepatitis or cirrhosis.

LABORATORY DIAGNOSIS

The laboratory tests used in the diagnosis of acute delta co-infection, superinfection and chronic delta hepatitis are given on Table 1.

Address for Correspondence: Ramazan Idilman E-mail: idilman@medicine.ankara.edu.tr

Table 1. Laboratory diagnosis in delta hepatitis

Diagnostic markers	Acute HBV/HDV co-infection	HDV superinfection	Chronic HDV infection
HBsAg	Positive	Positive	Positive
Anti-HBc IgM	Positive	Negative	Negative
Serum HDAg	Early and of short duration, might be missed frequently	Early and of short duration, might be missed frequently	Cannot be identified
Serum HDV RNA	Early and transient but longer than HDAg	Early, continuous	Generally positive
Anti-HDV, total	Late, low titer	Rapidly rising titers	High titers
Anti-HDV, IgM	Transient, may be the only marker	Rapidly rising and permanent titers	Changing titers, generally high
Liver HDAg	Not indicated	Positive	Generally positive, can be negative during late phase

HBV: hepatitis B virus; HDV: hepatitis D virus; HBsAg: hepatitis B surface antigen; Anti-HBc: antibody to hepatitis B core antigen; IgM: immunoglobulin M; HDAg: hepatitis delta antigen; RNA: ribonucleic acid

LABORATORY DIAGNOSIS OF HEPATITIS D CO-INFECTION (ACUTE HDV INFECTION)

Most of the co-infections clinically resemble acute icteric HBV infection. HDV co-infection is characterized by an increase in IgM and IgG antibodies against HDV. Since the beginning of acute hepatitis, antibody response to HDV is slow. IgM antibody response to HDV is slow and can be delayed by days or even weeks. IgG antibody response is first seen during the convalescent phase. The confirming of HDV co-infection in HBsAg-positive patient may require a long-term follow-up (8-17). HBsAg, anti-HBc IgM, anti-HDV IgM and HDV ribonucleic acid (RNA) levels are all positive during co-infection.

LABORATORY DIAGNOSIS OF HEPATITIS D SUPERINFECTION

Serum ALT level does not usually have a biphasic course. When acute liver injury (ALT levels, 10 times or more the upper limit of normal range) develops in patients with known HBsAg positivity, anti-HDV should be investigated (8,10-14,16).

In HBsAg-positive, anti-HBc IgM-negative patients, the detection of one of the following tests; anti-HDV IgM antibody or a detectable HDV RNA level establishes the diagnosis of delta superinfection.

LABORATORY DIAGNOSIS OF CHD INFECTION

In patients with HBsAg and total anti-HDV positivity of longer than six months, the positive serum HDV RNA by either qualitative or quantitative polymerase chain reaction (PCR) makes the diagnosis of CHD (11,18-22). HDV RNA testing remains the gold standard diagnostic testing for the diagnosis of HDV infection.

THE PROBLEMS IN THE DIAGNOSES OF ACUTE AND CHD INFECTION

The more widespread use of anti-HDV IgM measurements should be encouraged. AntiHDV IgM is useful and cheap serological marker for ongoing HDV infection. However, its sensitivity is lower than HDV RNA testing by PCR.

Hepatitis delta antigen test has a low sensitivity. In CDH infection, HDAg is in complex form with anti-HDV and cannot be readily identified with ELISA. Immunoblot assay is necessary to be used for HDAg detection, but it is very limited used in clinical practice (23).

The problem of HDV RNA standardization: There is a HDV RNA standard which was available since the end of 2013. World Health Organization (WHO) and Paul Ehrlich Institute are the leaderships and with one of the main contributors in its development being the Hepatology Institute of the Ankara University. Laboratories should obtain this standard. Even though sensitivity and dynamic "range" differences might continue despite using this standard, provision of comparable measurements that are expressed in IU/mL instead of copy/mL would be possible.

Anti HDV testing: There is inadequacy of diagnostic value during the early stage as anti-HDV gets positive during the late stage.

Immunohistochemical detection of HDAg in liver tissue: It was used to establish the diagnosis of active HDV infection in the past (8,10-14,16).

THE RELATIONSHIP BETWEEN SERUM HBV DNA AND HDV RNA IN ACUTE HEPATITIS DELTA CO- AND SUPERINFECTIONS

In acute delta co-infection, the patients are confronted with HBV and HDV infection at the same time. This condition is considerably rare and happens due to infected syringes in intravenous drug users. Acute HBV-HDV co-infection may have a mild or severe course, and fulminant hepatitis can develop. In HDV co-infection, serological evidence of HBV may be detected first since HDV infection starts after HBV infection. Two peaks of transaminase elevations may be observed during the course of acute hepatitis; the first peak is general related with HBV, whereas the second is related with HDV (11). Similarly, serum HBV DNA is firstly detected and followed by serum HDV RNA positivity. However, in some cases, acute HDV-HBV co-infection cannot be differentiated from acute hepatitis B mono-infection

on clinical grounds. Acute delta co-infection will lead to eradication of both viruses in the vast majority of cases. In less than 5% of cases patients may develop chronic hepatitis.

In acute delta superinfection, HBV DNA became negative in chronic HBsAg carriers. In approximately 10% of the cases, it may lead to clearance of HDV, and even HBsAg. In CHD, typically HDV suppresses HBV although a shift of the dominant virus over time is possible and has been reported previously (10,11,13,14).

THE RELATIONSHIP BETWEEN HBV DNA AND HDV RNA IN CHD INFECTION

Hepatitis D virus typically suppresses HBV in patients with CHD. Serum HDV RNA levels are high, whereas serum HBV DNA levels is either positive with low titers or below measurable levels.

Serologically, HBeAg is negative and anti HBe is positive in more than 80% of the cases. In HBeAg-positive CHD, HBV DNA levels are generally higher than HBeAg-negative CHD. However, serum HDV RNA is positive with high level (24,25). HBsAg levels do not directly correlate with serum HBV DNA level in HBeAg-negative CDH patients, however, HBsAg production is preserved (26).

On the other hand, despite being uncommon, there are cases reported high titers of HBV DNA and HDV RNA positivity. AASLD guideline is recommended adding NA treatment to pegylated interferon treatment in such cases (27).

TREATMENT FOR AHD INFECTION

No specific treatment is recommended in treatment of acute HDV infection. Supportive treatment is recommended. Patients who have a tendency towards a fulminant course should preferably be followed-up at liver transplantation (LT) center (27-29).

TREATMENT FOR ACUTE FULMINANT HDV INFECTION

Mortality rates are very high in patients with acute fulminant HDV infection. Specific antiviral treatment is not available (20-23). Supportive treatment is recommended. Infection, hepatic encephalopathy and coagulopathy should be managed. The fulminant cases should be followed-up at LT centers (20-23).

TREATMENT PATIENTS WITH CDH

Chronic delta hepatitis treatment has not changed since 1980's. Interferons are the only effective treatment based on the perspective of evidence-based medicine. Currently, pegylated interferons (PegIFNs) alpha 2a or 2b are used in the treatment of CDH, instead of classical interferons. The treatment is basically not different from PegIFN treatment of CHB. The treatment duration is one year. Various studies have been performed with the hypothesis that two years of treatment would be superior to one, but these did not yield the anticipated results. Meanwhile, expert opinions and certain case presentations and some previous studies suggested that that some patients might be benefit from long-term treatment (30-33). In a retrospective study focusing on the delta hepatitis database of Ankara University School of Medicine, increasing the duration of treatment was shown to increase cumulative treatment response rates as well (33). Here, it is obvious that there is the need to successfully identify CDH patients who do not respond to treatment. If patients do not have more than 1 $\log_{10}$ IU/mL decrease in serum HDV RNA in the sixth month of treatment, the possibility of non-response to treatment is high (34). For those who have at least 2 $\log_{10}$ IU/mL of a decrease in HDV RNA at the end of treatment or who become negative at the end of the treatment and recurrence again, the logical approach seems to be continuing the antiviral treatment without stopping or reinitiating at the time of a recurrence. During recent years, studies performed on humans with prenylation inhibitors (35), hepatocyte entry inhibitors (36) and nucleic acid polymers (37) seemed promising for the near future.

Patients who respond to treatment have lower rates of developing cirrhosis, lower need to LT and lower hepatic disease-related mortality compared to those who do not respond (33).

Contraindications, side effects and monitorization of PegIFN treatment is similar to what is applied during the course of CHB infection. Patients should be closely monitored during interferon treatment for severe ALT exacerbations. Although some studies reported that interferon treatment can be safely used in patients with compensated cirrhosis (38), decompensation might develop during the treatment.

Lamivudine, ribavirin and famciclovir have lack efficacy in treatment of CDH (39-44).

RESPONSE TO ANTIVIRAL TREATMENT

Biochemical response:

Total response: Normalization of serum ALT levels

Virological response:

Total response: HDV RNA decreasing to undetectable levels

Partial response: HDV RNA decreasing by at least one log compared to baseline level

Histological response: Decrease in inflammation (≥2 points) and fibrosis (1 points)

Biochemical and virological responses should be firstly evaluated during the treatment. In a successful treatment course for CHD, a loss of HDV RNA should be followed by loss of HBsAg and development of anti-HBs positivity. However, this aim is very difficult to reach, especially, HBsAg loss. However, HBsAg negativity can be seen in mean time in CDH patients with permanent viral response (33). The most rational criteria for

a successful treatment response is HDV RNA negativity that persists after discontinuation of treatment. When using interferon treatment for hepatitis C, having a virological response 6 months after the discontinuation of treatment is regarded as a permanent response and a cure; yet this algorithm was not shown to be true for CDH. In the HIDIT-1 study, 16 CDH patients had HDV RNA negative 6 months after stopping treatment; 9 of them were shown to be positive for HDV RNA at least for once during the follow-up period (45). Therefore, after the discontinuation of treatment, the CDH patients treated with PegIFN should be followed-up for three years for a possible recurrence. In this case, ongoing virological response was defined, instead of permanent virological response (33).

Serum aminotransferases levels should be monitored with monthly intervals. Virological response should be monitored at 3-6-month intervals.

The combination treatments performed so far have not been shown as more effective than interferon treatment alone (39,41-44,46). However, with new treatments currently under investigation in phase 2 studies combination treatment may become a viable option (47).

TREATMENT FOR CDH PATIENTS WITH NORMAL ALT LEVELS AND DETECTABLE HDV RNA LEVEL

Serum HDV RNA testing should be repeated in patients with normal ALT and detectable HDV RNA levels. This test has high false positivity and negativity rates. When HDV RNA positivity is confirmed, liver biopsy should be performed to evaluate the severity and prognosis of liver disease. Delta hepatitis nearly always has a severe disease course and poor prognosis; therefore PegIFN treatment is recommended regardless of histological findings. The treatment is not different than those of other patients with CDH.

TREATMENT FOR PATIENTS WITH COMPENSATED CIRRHOSIS

Pegylated interferons treatment can be initiated with close follow-up. The risk of development of interferon-related side effects and decompensation are high (18,48). If necessary, PegIFN dose adjustment should be considered. Several cases reported in the literature that interferon alpha treatment improved liver histology in patients with compensated cirrhosis (46). Notably, in the HIDIT-2 Study, virological response rates in cirrhotic patients were similar to non-cirrhotic patients.

TREATMENT FOR RECIPIENTS WITH HDV INFECTION WHO HAD RELAPSE AFTER LT

No treatment is available to prevent the development of HDV relapse after LT. HBV and HDV markers should be monitored after LT. Management of HBV relapse after LT would also have a positive impact on the course of HDV infection (49). Latent HDV infection has been reported post-transplant which carries the risk of being "rescued" by HBV (50).

TREATMENT FOR HDV INFECTION IN PATIENTS WITH SLE, DIABETES MELLITUS AND CHRONIC RENAL FAILURE

The expression of type 1 interferon-regulated genes is increased in patients with systemic lupus erythematosus (SLE). Further, cases of IFN-induced rheumatic disease exist (51,52). The use interferon treatment in patients with HDV infection in the setting of SLE or any rheumatic disease can pose a difficult clinical decision. Managing the more severe disease represents a reasonable compromise. PegIFN treatment may be considered under close follow-up in CDH patients, who have remission rheumatic disease.

For patients with diabetes mellitus, interferon treatment is recommended in the treatment of CDH (53,54). The treatment approaches of CDH in patients with chronic renal failure should be approached as that of chronic HBV infection (55-57).

THE MOLECULAR TESTS USED IN DIAGNOSIS AND THE SELECTION OF REFERENCE LABORATORIES

Quantitative measurement of HDV RNA is the the gold standard test to evaluate treatment efficacy and follow-up in CDH patients treated with PegIFN. The absence of commercial kits that would be widely used for this purpose is a significant shortcoming. The reference laboratories should obtain the standard kits which would enable them to have comparable measurements expressed in IU/mL.

Quantitative measurement of HBsAg titer is another test to be used in the treatment and follow-up of CDH. This test should be performed at 6 months of PegIFN treatment. For example, from baseline, no any decrease in HBsAg levels is associated with treatment unresponsiveness (34).

TREATMENT FOR CDH PATIENTS DURING EXACERBATION

Chronic delta hepatitis patients with exacerbations should be closely followed-up for liver failure. LT should be performed when it is indicated (17,18,23,25,26,58).

In instances of disease exacerbation after discontinuation of treatment, the most suitable approach would be to retreat with PegIFN treatment if there is no contraindication.

HDV SCREENING

In Turkey, anti-delta antibody test should be recommended in all the HBsAg-positive patients. Anti-delta antibody test should be recommended in case of an acute hepatic exacerbation.

TREATMENT FOR PATIENTS WITH TRIPLE INFECTIONS (CHB+CHC+CHD)

In triple infections, HDV is the dominant virus in European studies, whereas HCV is the dominant virus in Asian studies (24,58-61). The chronology of acquiring virological infections can as well be of importance. The last acquiring virus has not been reported to suppress the previous virus or viruses (62). Dominant virus can also change its place in time (63,64). In general, the prognosis of triple virus infection is worse than a mono-infection.

The treatment should first be directed at the dominant virus; this would be in the form of PegIFN treatment for HDV infection in the most of the cases (16). The suppressed virus can be reactivated during treatment. Reactivated virus should also be treated. Currently, as both HBV and HCV can be successfully treated with oral antiviral agents without having serious side effects. When HDV is being treated, one might consider giving antiviral treatment for HCV as well.

In Conclusion:

- All patients with compensated cirrhosis with high serum ALT levels and detectable HDV RNA level should be treated. Liver biopsy is not necessary.
- In instances where serum HDV RNA is negative despite high serum ALT level, HDV RNA testing should be repeated. If HDV RNA is negative, other causes of liver diseases should be investigated.
- PegIFN treatment is used in the treatment of CDH. Treatment dose is same the dose for CHB. Treatment duration should be at least one year.
- NAs treatment is recommended in CDH patients, who have HBV replication.
- PegIFN treatment is contraindicated in decompensated cirrhotic patients.

The authors declare no conflicts of interest; no financial support was received for the conduct of this study.

Acknowledgments

The authors thank Elif Sertesen and Şule Girmen for their kind assistance in English grammar edition.

REFERENCES

1. Smedile A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. Lancet 1982; 2: 945-7. [CrossRef]
2. Govindarajan S, Chin KP, Redeker AG, Peters RL. Fulminant B viral hepatitis: role of delta agent. Gastroenterology 1984; 86: 1417-20.
3. Buti M, Homs M, Rodriguez-Frias F, et al. Clinical outcome of acute and chronic hepatitis delta over time: a long-term follow-up study. J Viral Hepat 2011; 18: 434-42. [CrossRef]
4. Yurdaydin C, Idilman R. Therapy of delta hepatitis. Cold Spring Harb Perspect Med 2015; 5: a021543. [CrossRef]
5. Yurdaydın C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. J Viral Hepat 2010; 17: 749-56. [CrossRef]
6. Rizzetto M, Verme G, Recchia S, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. Ann Intern Med 1983; 98: 437-41. [CrossRef]
7. Manesis EK, Papatheodoridis GV, Tiniakos DG, et al. Hepatitis B surface antigen: relation to hepatitis B replication parameters in HBeAg-negative chronic hepatitis B. J Hepatol 2011; 55: 61-8. [CrossRef]
8. Casey JL. Hepatitis delta virus: Molecular biology, pathogenesis and immunology. Antivir Ther 1998; 3: 37-42.
9. Jardi R, Buti M, Cotrina M,et al. Determination of hepatitis delta virus RNA by polymerase chain reaction in acute and chronic delta infection. Hepatology 1995; 21: 25-9. [CrossRef]
10. Hoşoğlu S. Hepatit D Virus enfeksiyonunun kliniği ve tanısı. Balık İ, Tabak F ve Tekeli E, editors. Viral Hepatit 2007, Viral Hepatitle Savaşım Derneği. İstanbul: Oben Matbaası; 2007.p.273-4.
11. Mıstık R. Viral hepatitler " Klinisyenler için laboratuar tanı rehberi". Ulukaya E, editor. İstanbul: Nobel ve Güneş Kitabevi; 2004: 639-65.
12. Mıstık R. Akut viral hepatitler. Memik F editor. Klinik Gastroenteroloji. Bursa: Nobel ve Güneş Kitabevi; 2004.p.558-77.
13. Modahi LE, Lai MM. Hepatitis delta virus: The molecular basis of laboratory diagnosis. Crit Rev Clin Lab Sci 2000; 37: 42-92.
14. Schaper M, Rodriguez-Frias F, Jardi R, et al. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. J Hepatol 2010; 52: 658-64. [CrossRef]
15. Rizzetto M. Hepatitis D: Virology, clinical and epidemiological aspects. Acta Gastroenterol Belg 2000; 63: 221-4.
16. Ryder SD, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system: Acute hepatitis. BMJ 2001; 322: 151-3. [CrossRef]
17. Negro F, Rizzetto M. Diagnosis of hepatitis delta virus infection. J Hepatol 1995; 22: 136-9.
18. Gürel S. Kronik viral hepatitler. Memik F editor. Klinik Gastroenteroloji. Bursa: Nobel ve Güneş Kitabevi; 2004.p.578-89.
19. Huang YH, Wu JC, Sheng WY, Huo TI, Chang FY, Lee SD. Diagnostic value of anti-hepatitis D virus (HDV) antibodies revisited: a study of total and IgM anti-HDV compared with detection of HDV-RNA by polymerase chain reaction. J Gastroenterol Hepatol 1998; 13: 57-61. [CrossRef]
20. Rizetto M, Durazzo M. Hepatitis delta virus (HDV) infections, epidemiological and clinical heterogeneity. J Hepatol 1991; 13: 116-8. [CrossRef]
21. Rosina F, Rizzetto M. Hepatitis D virus, epidemiology and, natural history. Thomas HC, Lemon S, Zuckerman AJ, editors. Viral Hepatitis. Oxford: Blackwell Publishing; 2005.p.583-9.
22. Perillo R, Nair S. Hepatitis B and D. Gastrointestinal and Liver Disease. Sleisenger M, Fordtran JS, editors. Philadelphia: WB Saunders Company; 2007.p.1647-79.
23. Pascarella S, Negro F. Hepatitis D virus: an update. Liver Int 2011; 31: 7-21. [CrossRef]
24. Jardi R, Rodriguez F, Buti M, et al. Role of hepatitis B, C and D viruses in dual and triple ınfection: influence of viral genotypes and hepatitis B precore and basal core promoter mutations on viral replicative interference. Hepatology 2001; 34: 404-10. [CrossRef]
25. Heidrich B, Serrano BC, Idilman R, et al. HBeAg-positive hepatitis delta: virological patterns and clinical long-term outcome. Liver Int 2012; 32: 1415-25. [CrossRef]
26. Kabaçam G, Wedemeyer H, Savaş B, et al. Role of immunohistochemistry for hepatitis D and hepatitis B virus in hepatitis delta. Liver Int 2014; 34: 1207-15. [CrossRef]
27. Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatology 2007; 45: 507-39. [CrossRef]
28. Hsieh TH, Liu CJ, Chen DS, Chen PJ. Natural course and treatment of hepatitis D virus infection. J Formos Med Assoc 2006; 105: 869-81. [CrossRef]
29. Yalçın K. Hepatit Delta Virüs İnfeksiyonunda Klinik Özellikler ve Tanı. Türkiye'de Hepatit Delta Virüs İnfeksiyonu Kitabı, Karaciğer Araştırmaları Derneği. 2005.p.52-66.

30. Lau DT, Kleiner DE, Park Y, Di Bisceglie AM, Hoofnagle JH. Resolution of chronic delta hepatitis after 12 years of interferon alfa therapy. Gastroenterology 1999; 117: 1229-33. [CrossRef]
31. Heller T, Rotman Y, Koh C, et al. Long-term therapy of chronic delta hepatitis with peginterferon alfa. Aliment Pharmacol Ther 2014; 40: 93-104. [CrossRef]
32. Soyer OM, Baran B, Ormeci AC, et al. Comparison of the efficacy of 12 months and longer courses of interferon therapy for the treatment of chronic delta hepatitis: a retrospective cohort study. Postgraduate Med 2016; 128: 432-8. [CrossRef]
33. Yurdaydin C, Keskin O, Kalkan C, Karakaya F, Caliskan A, et al. Interferon treatment duration in patients with chronic delta hepatitis and its effect on the natural course of the disease. J Infect Dis 2017
34. Keskin O, Wedemeyer H, Tüzün A, et al. Association between level of hepatitis D virus RNA at week 24 of pegylated ınterferon therapy and outcome. Clin Gastroenterol Hepatol 2015; 13: 2342-9. [CrossRef]
35. Koh C, Canini L, Dahari H, et al. Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial. Lancet Infect Dis 2015; 15: 1167-74. [CrossRef]
36. Bogomolov P, Alexandrov A, Voronkova N, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. J Hepatol 2016; 65: 490-8. [CrossRef]
37. Al-Mahtab M, Bazinet M, Vaillant A. Safety and efficacy of nucleic acid polymers in monotherapy and combined with ımmunotherapy in treatment-naive Bangladeshi patients with HBeAg+ chronic hepatitis B infection. PLoS One 2016; 11: e0156667. [CrossRef]
38. Kabaçam G, Dalekos GN, Çakaloğlu Y, et al. Pegylated interferon based treatment in patients with advanced liver disease due to chronic delta hepatitis. Turk J Gastroenterol 2012; 23: 560-8. [CrossRef]
39. Gunsar F, Akarca US, Ersoz G, et al. Two-year interferon therapy with or without ribavirin in chronic delta hepatitis. Antivir Ther 2005; 10: 721-6.
40. Lau DT, Doo E, Park Y,et al. Lamivudine for chronic delta hepatitis. Hepatology 1999; 30: 546-9. [CrossRef]
41. Niro GA, Ciancio A, Gaeta GB, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. Hepatology 2006; 4: 713-20. [CrossRef]
42. Yurdaydin C, Bozkaya H, Gürel S, et al. Famciclovir treatment of chronic delta hepatitis. J Hepatol 2002; 37: 266-71. [CrossRef]
43. Wolters LM, von Nunen AB, Honkoop P, et al. Lamivudine-high dose interferon combination therapy for chronic hepatitis B patients co-infected with hepatitis D virus. J Viral Hepat 2000; 7: 428-34. [CrossRef]
44. Niro GA, Ciancio A, Tillman HL, et al. Lamivudine therapy in chronic delta hepatitis: a randomized controlled pilot study. Aliment Pharmacol Ther 2005; 22: 227-32. [CrossRef]
45. Heidrich B, Yurdaydın C, Kabaçam G, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology 2014; 60: 87-97. [CrossRef]
46. Canbakan B, Senturk H, Tabak F, et al. Efficacy of interferon alpha-2b and lamivudine combination treatment in comparison to interferon alpha-2b alone in chronic delta hepatitis: a randomized trial. J Gastroenterol Hepatol 2006; 21: 657-63. [CrossRef]
47. Yurdaydin C, Keskin O, Kalkan Ç, et al. Optimizing lonafarnib treatment for the management of chronic delta hepatitis: the LOWR HDV-1 Study. Hepatology. 2017 November 20. doi: 10.1002/hep.29658. [Epub ahead of print] [CrossRef]
48. Farci P, Roskams T, Chessa L, et al. Long-term benefit of ınterferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. Gastroenterology 2004; 126: 1740-9. [CrossRef]
49. Terrault N, Roche B, Samuel D. Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. Liver Transpl 2005; 11: 716-32. [CrossRef]
50. Mederacke I, Filmann N, Yurdaydin C, et al. Rapid early HDV RNA decline in the peripheral blood but prolonged intrahepatic hepatitis delta antigen persistence after liver transplantation. J Hepatol 2012; 56: 115-22.[CrossRef]
51. Rönnblom L, Alm GV. Systemic lupus erythematosus and the type I interferon. Arthritis Res Ther 2003; 5: 68-75. [CrossRef]
52. Thibault DL, Utz PJ. Interpreting interest in interferon-alpha. Arthritis Res Ther 2003; 5: 246-8. [CrossRef]
53. Decock S, Verslype C, Fevery J. Hepatitis C and insulin resistance: mutual interactions. Acta Clin Belg 2007; 62: 111-9. [CrossRef]
54. Soultati AS, Dourakis SP, Alexopoulou A, Deutsch M, Archimandritis AJ. Simultaneous development of diabetic ketoacidosis and Hashitoxicosis in a patient treated with pegylated interferon-alpha for chronic hepatitis C. World J Gastroenterol 2007; 13: 1292-4. [CrossRef]
55. Amarapurkar DN, Patel ND, Kirpalani AL. Monotherapy with peginterferon alpha-2b {12 kDa} for chronic hepatitis C infection in patients undergoing haemodialysis. Trop Gastroenterol 2007; 28: 16-8.
56. Espinosa M, Arenas MD, Aumente MD, et al. Anemia associated with pegylated interferon-alpha 2a and alpha 2b therapy in hemodialysis patients. Clin Nephrol 2007; 67: 366-73. [CrossRef]
57. Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepat 2007;14: 697-703. [CrossRef]
58. Farci P. Treatment of chronic hepatitis D: New advances, old challenges. Hepatology 2006; 44: 536-9. [CrossRef]
59. Mathurin P, Thibault V, Kadidja K, et al. Replication status and histological features of patients with triple (B, C, D) and dual (B, C) hepatic infections. J Viral Hepat 2000; 7: 15-22. [CrossRef]
60. Liaw YF, Tsai SL, Sheen IS, et al. Clinical and virological course of chronic hepatitis B virus infection with hepatitis C and D virus markers. Am J Gastroenterol 1998; 93: 354-9. [CrossRef]
61. Lu SN, Chen TM, Lee CM, Wang JH, Tung HD, Wu JC. Molecular epidemiological and clinical aspects of hepatitis D virus in a unique triple hepatitis viruses (B, C, D) endemic community in Taiwan. J Med Virol 2003; 70: 74-80. [CrossRef]
62. Gaeta GB, Precone DF, Cozzi-Lepri A, Cicconi P, D'Arminio Monforte A. Multiple viral infections. J Hepatol 2006; 44: 108-13. [CrossRef]
63. Boyd A, Lacombe K, Miailhes P, et al. Longitudinal evaluation of viral interactions in treated HIV hepatitis B co-infected patients with additional hepatitis C and D virus. J Viral Hepat 2010; 17: 65-76. [CrossRef]
64. Liaw YF, Yeh CT, Tsai SL. Impact of acute hepatitis B virus superinfection on chronic hepatitis C virus infection. Am J Gastroenterol 2000; 95: 2978-80. [CrossRef]