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Mini-Review

Side effects of antiviral drugs used for the treatment of HBV/HDV viruses from a multidisciplinary perspective

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ABSTRACT

Approximately 2 billion people worldwide show exposure to the virus, and nearly 257 million people carry a Hepatitis B Virus (HBV) chronic infection. Today, HBV treatment remains challenging and new treatments are in the pipeline and ready for the next future. In this review, we summarize the side effects of the approved drugs for HBV/HDV treatment (including new treatments) focusing on the cutaneous ones that have a higher overall prevalence in HBV-treated patients. Remarkably, the HBV/HDV co-infection may lead to the most severe form of viral hepatitis and interestingly treatment evidence for hepatitis D is still poor. Furthermore, HBV eradication is of fundamental importance to preventing hepatitis D. HBV eradication might be possible in the next future with the current armamentarium and development of new drugs; new studies should be performed to compare and rank the use of HBV/HDV drugs.

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KEYWORDS: Hepatitis B, Hepatitis D, Hepatitis delta virus, adverse effects.

INTRODUCTION

Hepatitis B Virus (HBV) treatment is challenging due to the natural history of infection, whose virus tends to integrate into the covalently closed-circular DNA (cccDNA) in the host organism's cells. Hence receiving immunosuppressive drugs [1]; thus, the treatment goal should be the HBV ccc-DNA eradication in human cells. The HBV ccc-DNA eradication cannot be measured in routine clinical practice, and hence the stable off-antiviral suppression of HBV viremia and HBsAg and normalization of transaminases are the surrogate goal of the therapy [2]. Hepatitis D virus (HDV) requires HBV for its replication; thus, HDV infection occurs only simultaneously or as HBV super-infection [3]. Indeed, the cornerstone of HDV treatment is the treatment of HBV.

The cornerstone of HBV/HDV treatment has been interferons for years with scarce success and a lot of collateral effects. Recently, with the introduction of

antivirals, there has been an improvement in therapeutic efficacy and a reduction in side effects. This review focuses on new antivirals for HBV and HDV treatment.

Epidemiology of HBV/HDV

HBV infection is a major public health problem in most countries. Approximately 2 billion people worldwide show exposure to the virus, and nearly 257 million people carry an HBV chronic infection. It is estimated that only 10% are aware of their carrier status. About 80-90% of children who contract the infection in the first year of life become chronic, while more than 90% of those who contract the infection in adulthood recover within six months of the onset of symptoms. Furthermore, in 2015 about 887,000 people died due to HBV consequences [4]. Risk factors for HBV infection include transfusion of unscreened blood, sexual promiscuity, sharing or reusing syringes among injection drug users, tattooing, working or residing in a health-care setting, living in a correctional facility, renal dialysis, and long-term household or intimate non-sexual contact with a hepatitis B surface antigen (HBsAg)-positive individual. Vaccination is the most effective preventive measure [5]. The prevalence of chronic HBV infection is about 5% worldwide, but it differs between regions: 0.1%-2.0% in the United States and Western Europe, 2.0%-8.0% in Mediterranean countries and Japan, and 8.0%-20.0% in Southeast Asia and Sub-Saharan regions [6]. The highest incidence of chronic infections is reported in the WHO Western Pacific Region countries and Africa: 6.2% and 6.1% of adults infected, respectively. In the Eastern Mediterranean Region, Southeast Asia, and Europe, the percentages of subjects with chronic infections are estimated to be 3.3%, 2.0%, and 1.6%, respectively. In the Region of the Americas, the infected population is 0.7% [7, 8]. HDV infection can be transmitted either simultaneously with HBV infection (coinfection) or to people who are already chronic HBV carriers (super-infection). It has been estimated that 15-20 million people worldwide have a chronic HDV infection, with substantial geographical differences. In the general population, the global estimated anti-HDV prevalence was 4.5% among HBsAg-positive people and 0.16% overall, with regional estimates for HBsAg-positive people ranging from 3.0% in Europe to 6.0% in Africa. The global estimated anti-HDV prevalence in hepatology clinic populations was 16.4% among HBsAg-positive people, with estimates ranging from 3.3% in the Americas to 19.5% in Europe. Research from studies reporting HDV genotype data identifies that Genotype 1 predominates globally (89.9% of published data) [3]. As a consequence of the decrease in HBV endemicity, the spread of HDV infection has dramatically decreased in the last years [5, 9]; and it is foreseeable that given the impact of vaccination on the number of HBV subjects, the spread of HDV infection will decrease further in the coming years.

Patterns of HBV viral resistance

HBV and HDV co-infection causes the most severe form of viral hepatitis, leading to cirrhosis in 15% of cases within 1-2 years and 70-80% of cases within 5–10 years [10]. Chronic hepatitis B virus (HBV) infection continues to be a major health burden worldwide. Currently approved antiviral treatment options for chronic hepatitis B include interferon alpha2a, usually in its pegylated form (PEG-IFN) or nucleos(t)ide analogues (NAs). These treatments have been available for nearly 2 decades but do not eliminate the virus. PEG-IFN and NAs have been demonstrated to prevent cirrhosis, liver failure, and hepatocellular carcinoma (HCC), but the risk of HCC remains, even for patients in whom the virus is suppressed. Both therapies do not completely eradicate viral infection and promote severe side effects. Thus, the development of new effective treatments is imperative [11]. PEG-IFN acts with a direct antiviral mechanism, mainly by inducing the destruction of infected hepatocytes by the immune system; it has both antiviral and immunomodulatory activities, although the precise mechanisms of action remain unclear, burdened by frequent and sometimes disabling side effects, but without the emergence of resistance during treatment. Therapy with PEG-IFN-α has the advantages of finite treatment duration and higher rates of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) seroconversion, the absence of drug resistance, and an opportunity to obtain a durable post-treatment response to therapy, but the disadvantage of more

significant adverse effects. NAs act with a direct antiviral mechanism, suppressing the replication of the viral genome by selectively targeting the viral reverse transcriptase. The advantages of NAs are that it is an oral medication, are a potent antiviral, and have fewer adverse effects than interferon. The main disadvantage of NAs is that rates of HBeAg and HBsAg seroconversion are lower than interferons and sustained off-treatment responses are rare. As a result, the treatment duration is usually indefinite. Unfortunately, a long duration of NA treatment is associated with an increased risk of developing drug resistance, limiting, or canceling their effectiveness. Anti-HBV treatment with NAs, which began with lamivudine (LAM) in 1998, has resulted in remarkable improvements in the survival of patients with chronic hepatitis B and a reduced incidence of HCC. These results were documented with lamivudine, entecavir (ETV), and tenofovir (TNV) [12]. LAM, the earliest nucleoside for treatment of HBV, is characterized by a remarkable efficacy, but by a low genetic barrier to resistance, so that drug-resistant viral strains are observed in 60-70% of patients after one year of treatment [13]. Subsequently, another nucleoside ETV and the nucleotide TDF represent a valid alternative to LAM, since they were found to have much higher antiviral activity and much higher barriers to resistance. Indeed, in patients never treated with NA the risk of antiviral drug resistance is ≤1% after five years of continued treatment with ETV and eight years with TDF. But the emergence of resistance to LAM also limits the effectiveness of ETV and TDF. The risk of resistance to ETV is as high as 50% in patients with lamivudine-resistant HBV [14, 15].

Patterns of HDV viral resistance

For Hepatitis D, PEG-IFN represents the only available treatment option with low response rates (around 20%-30%). Although specific viral resistance in HDV infection has not been reported, it cannot be completely discarded. The paucity of potential virological therapeutic targets strongly hinders HDV antiviral treatment. New antiviral strategies are currently under study, and the possible emergence or selection of antiviral resistance is a concern, mainly due to the high genetic diversity of HDV [3, 16].

Approved treatment options for HBV/HDV

The current goal of hepatitis B therapy is to reduce the risk of progression to cirrhosis, the extra-hepatic complications, the development of HCC and prevent ongoing transmission. Currently, there are two different treatment strategies for both HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB) patients: treatment of finite duration with (PEG-)IFN and long-term treatment with nucleos(t)ide analogue (NA). PEG-IFN induces long-term immunological control with higher rates of HBeAg and HBsAg loss and without the risk of selection of resistant variants. The disadvantages of PEG-IFN therapy are less effective suppression of viral replication and the requirement of subcutaneous injection with adverse events including flu-like symptoms, myelosuppression, worsening of underlying mood disorders, and exacerbation of autoimmune conditions. It is also contraindicated in patients with pregnancy, decompensated cirrhosis, or severe exacerbations of hepatitis. For these reasons, PEG-IFN is not used widely in treatment. The NAs approved in Europe for HBV treatment include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (TBV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF); they can be classified into those with a low barrier (LAM, ADV, TBV) and those with high barrier to HBV resistance (ETV, TDF, TAF). Currently, therapy with LAM, TBV, or ADV is no more recommended due to the low genetic barrier and to the high percentage of virological mutations (>60% for LAM after 5 years, 10-20% for TBV after 2 years and up to 29% for ADV after 5 years). ETV, TDF and TAF seem to have a therapeutic profile with high efficacy and tolerability. TAF, the last NA approved in the treatment of CHB, is a prodrug of TDF that has demonstrated antiviral efficacy similar to TDF but at a lower dose with less long-term consequences on kidney and bone. The decision to initiate therapy depends upon the presence or absence of cirrhosis or advanced fibrosis, HBeAg and HBeAb status, level of HBV DNA, and aminotransferase levels. There are four important clinical practice guidelines for CHB: the 2018 American Association for the Study of Liver Diseases (AASLD) [17], the 2017 European Association for the Study of the Liver (EASL) [18], the 2015 Asia Pacific

Association for the Study of the Liver (APASL) [19], and the 2019 WHO Guidelines [20]. In patients with CHB, non-cirrhotic, recommendations from AASLD and APASL use a HBV DNA threshold of 20.000 IU/mL in HBeAg-positive, whereas EASL uses a lower threshold of 2000 IU/mL. Similarly, AASLD and APASL use a threshold of ALT 2x ULN, whereas EASL accepts > ULN. In HBeAg-negative CHB patients, AASLD, APASL and EASL guidelines accept a lower threshold for HBV DNA of 2000 IU/mL. AASLD and APASL continue to use the ALT threshold of 2× ULN, whereas EASL accepts > ULN. AASLD, APASL and EASL continue to recommend that patients with a histological examination showing moderate inflammation and fibrosis, or significant fibrosis should be treated. WHO recommendations do not distinguish HBeAg status; they use the same variables of HBV DNA, ALT and fibrosis assessment and state that non-cirrhotic patients over the age of 30 with persistently abnormal ALT and HBV DNA > 20 000 IU/mL are at risk of disease progression, and hence should be recommended for antiviral therapy. EASL tends to consider treatment in individuals older than 30, with persistently normal ALT and high HBV DNA levels, regardless of fibrosis stage. AASLD recommends NAs for CHB patients >40 years old with normal ALT, a viral load >1 000 000 IU/mL and significant necroinflammation or fibrosis. AASLD and WHO do not recommend antiviral therapy for immune-tolerant CHB. EASL allows therapy in CHB patients with a family history of HCC, cirrhosis or extrahepatic manifestations. In compensated cirrhosis, APASL uses a HBV DNA >2000 IU/mL to start therapy, whereas AASLD, EASL and WHO accept any detectable level of HBV DNA. For decompensated cirrhosis, all guidelines agree that antiviral therapy should be started with any detectable HBV DNA. In patients with HBV-HDV co-infection the ideal endpoint would be the clearance of both HBV and HDV infections from the liver, translating into anti-HBs seroconversion, to prevent liver disease progression. IFN-based therapies are the only currently approved treatment. Combination therapy with PEG IFN and NA (ETV, TDF, or TAF) is suggested in patients with high levels of HBV-DNA in AASLD guidelines. APASL suggests determining which virus is dominant, and in patients with high levels of HDV-RNA the treatment with PEG IFN alfa (without NA) for 12-18 months with monitorization for 6-12 months post-therapy is suggested. EASL considers levels of HBV-DNA; patients with ongoing HBV replication should be considered for NA therapy. The WHO does not make any recommendations for HBV-HDV coinfection due to the lack of data. In a clinical trial conducted by Farci *et al*. in the 1990s on 42 patients with CHD treated with IFN alpha-2a, they were divided into three groups: 9 million IU 3 times per week (high-dose), 3 million IU 3 times per week (low-dose), or no therapy for 1 year (control). A complete response was defined by normalization of ALT and negative HDV -RNA at the end of treatment; this was achieved by 50% of patients in the high-dose IFN group. In the low-dose group, 21% of patients had a complete response while 0% of the patients in the no-therapy group had a complete response. During a follow-up period of up to 48 weeks after therapy, all patients were found to have relapsed [21]. In a subsequent analysis of the same cohort, with follow-up period of 14 years after therapy, survival was significantly longer for patients who received high-dose IFN compared to patients who received low-dose IFN or patients who did not receive any therapy. Notably, achieving a 2 $\log_{10}$ decline in HDV RNA at the end of treatment was associated with the significant increase in survival. There was no difference in long-term outcomes between the low-dose IFN group and the no-therapy group, neither of which achieved the mean 2 $\log_{10}$ decrease in HDV RNA at the end of treatment [22]. With the efficacy of peginterferon in other viral hepatitis infections, and the FDA approval of peginterferon alfa-2b in 2001 for chronic hepatitis C, it was then explored for use in chronic HDV infection. Peginterferon alfa-2b was administered at 1.5 ug/kg/wk for 1 year with treatment success (defined as undetectable HDV RNA) in 57% of patients; however, after a median post-therapy follow-up of 16 months, the sustained virologic response rate was 43%. Prolonged peginterferon monotherapy has been studied for 72 weeks which resulted in low-level or undetectable HDV RNA in 34% of patients at the end of therapy and only in 21% of patients at 24 weeks of post-therapy follow-up. Long-term peginterferon alfa-2a with increasing doses up to 360 mcg/wk

has been studied for up to 5 years; however, this has not resulted in improved response rates; only 30% of patients achieved a complete virologic response, described as HDV RNA negativity and HBsAg seroconversion [22]. The effects of different durations of PegIFN alpha-2b therapy, and combinations with other drugs, were evaluated in patients with chronic HDV infection. Combination therapies with PegIFN alpha have been investigated, without much success. The combination of ribavirin with PegIFN alpha for 48 weeks followed by PegIFN monotherapy for an additional 24 weeks did not improve patient outcomes, compared to PegIFN monotherapy for 72 weeks. Nucleos(t)ide analogue therapy alone has shown no benefit, and combination of nucleos(t)ide analogue with PegIFN did not provide any benefit compared with PegIFN monotherapy [23].

New treatments in the pipeline

Several new agents are in the pipeline for the management of HBV and HDV infections. Entry inhibitors act on the sodium taurocholate cotransporting polypeptide (NTCP) that is a cellular receptor for viral entry of HBV and HDV into the hepatocytes [24, 25]. Bulevirtide (phase-2), formerly known as Myrcludex B (MYR), is the first-in-class agent. In a randomized pilot study, it was evaluated on 24 HBV/HDV-coinfected patients. Patients were randomized (1:1:1) to receive MYR, or Peg-IFN α-2a or their combination. HBV-DNA was significantly reduced at week 24 in the MYR plus Peg-IFN-α-2a arm. HDV-RNA significantly declined at week 24 in all arms. In 5 out of 8 patients of MYR plus Peg-IFN-α-2a arm an HDV-RNA negativization was observed compared to 2 patients each in the monotherapy arms. Overall, HBV and HDV kinetic studies showed a synergistic effect of combination therapy with MYR plus Peg-IFNα-2a on both viruses [26]. In another randomized trial, MYR plus Peg-IFNα-2a combination was associated with a significant reduction of HDV-DNA and normalization of ALT levels at week 72, and 40% (12 out of 30 patients) of treated patients had treatment success (defined as HDV-RNA undetectable). Moreover, 4 out of 15 patients (27%) treated with 2 mg MYR plus Peg-IFNα-2a had undetectable HBsAg levels and 3 out of 4 patients experienced HBsAg seroconversion [27]. RNA interference (RNAi) agents interfere and destroy viral messenger RNA (mRNA) [28]. JNJ-3989 (phase-2), formerly ARO-HBV, contains two RNAi that silence all mRNAs that are formed from episomal cccDNA and host integrated HBV-DNA. Multiple doses of JNJ-3989 plus a nucleos(t)ide analogue (NUC) was associated with a rapid and prolonged decline of HBsAg levels and other viral products [29]. JNJ-3989 is active against *naïve*- and *experienced*-NUC patients and in both HBeAg-positive and HBeAg-negative patients [30]. Similarly, Vir-2218 (phase-2), formerly ALN-HBV02, determines a substantial reduction of the HBsAg level in both HBeAg-positive and HBeAg-negative patients and across all dose levels [31]. Additional investigational RNAi agents are in preclinical (ALG-125097, BB-103) and clinical (AB-729 [phase-1], RG-6346 [phase-2], GSK-3228836 [phase-2], GSK-3389404 [phase-2]) stage of development, while others have been discontinued (ARB-1467, ARC-520, RG-6004). Capsid Assembly Inhibitors (CAIs) including capsid-assembly modulators and core-protein binding agents interfere with the proper HBV core assembly (aberrant capsids or morphologically normal capsids without genetic material) [32]. In early studies, ABI-H0731 (phase-2), formerly Vebicorvir, has demonstrated effective antiviral activity against HBV. ABI-H0731 plus entecavir (ETV) association appears to decrease viral DNA faster compared to NUC monotherapy. Moreover, ABI-H0731 inhibits cccDNA formation and has a pan genotypic activity, including genotypes A, B, C, and D. It is currently being further evaluated in phase 2 clinical trials [33]. Overall, ABI-H0731 shows a good profile of tolerability [34]. JNJ-56136379 (phase-2) is another CAI with a potent antiviral activity against HBV. A phase-2 trial evaluating JNJ-56136379 monotherapy and NUC combination is ongoing (NCT03361956). Overall, in a phase-1 study, all doses tested of JNJ-6379 were well tolerated [35]. Additional investigational CAI agents are in preclinical (GLP-26, AB-836) and clinical (ABI-H3733 [phase-1], ALG-000184 [phase-1], JNJ-0440 [phase-1], NVR-3778 [phase-1], RG-7907 [phase-1], ZM-H1505R [phase-1], ABI-H2158 [phase-2], EDP-514 [phase-2], Morphothiadine [phase-2]), QL-007 [phase-2]) stage of development, while others have been discontinued (AB-506). Another class in development

is that of HBsAg Inhibitors (sAgI). This class interferes with the production of HBsAg. The following agents are in clinical development: REP-2139 (phase-2), and REP-2165 (phase-2). ALG-020572 is another agent in the preclinical phase of development. In an open-label phase 2 study, enrolling HBV infected (HBeAg-negative) patients, REP-2139 or REP-2165 in association with tenofovir disoproxil fumarate (TDF) and Peg-IFNα-2a significantly increased the rate of HBsAg loss and HBsAg seroconversion compared to control group in which the patients were treated only with TDF *plus* Peg-IFNα-2a [36]. In recent years, novel NUCs have been approved outside the USA and Europe (Clevudine, Besifovir Dipivoxil Maleate) and others are in clinical development (ATI-2173 [phase-1] and CMX-157 [phase-2]). CMX-157, formerly Tenofovir Exalidex, is a prodrug of TDF, shows a similar efficacy of TDF and has demonstrated the potential for low systemic exposure, thereby reducing renal and bone alterations [37]. Several indirect-acting antivirals and immunotherapeutic are in development. Nitazoxanide (phase-1), an antiparasitic agent, inhibits the interaction of HBV regulatory protein X (HBx) with the host protein DNA damage-binding protein 1 (DDB1) [38]. EYP001 (phase-2) is a synthetic non-steroidal, non-bile acid farnesoid X receptor (FXR) agonist that inhibits the secretion of HBV-DNA and the HBV antigens HBsAg and HBeAg [39]. Two phase-2 studies evaluated the efficacy of EYP001: NCT04465916 assesses the safety and anti-viral effect in CHB patients in combination with NA (ETV or TD) compared to Placebo + NA alone and NCT04365933 assesses the safety and anti-viral effect of EYP001 administered in combination with ETV and peg-IFN or only with peg-IFN. Immunotherapeutics in development include toll-like receptor (TLR)-7 (RG-7854 [phase-1], AL-034 [phase-1], RO-7020531 [phase-2]), TLR-8 (GS-9688 [phase-2], SBT-8230 [preclinical stage]), Checkpoint inhibitors (GS-4224 [phase-1] and Envafolimab [phase-2]), Apoptosis Inducer (APG-1387 [phase-2]), and T lymphocyte stimulants (IMC-I109V phase-1)]. Finally, for HBV management, several monoclonal antibodies (Vir-3434 [phase-1] and Lenvervimab [phase-2]) and therapeutic vaccines are in preclinical and clinical stage of development. Regarding HDV, other than the above-mentioned MYR that was recently approved in Europe for the treatment of viremic HDV patients, still other agents are in development. Lonafarnib (LNF) is a first-in-class inhibitor of farnesyltransferase, an enzyme involved in the modification of proteins through a process called prenylation. LNF inhibits the prenylation step of HDV replication inside liver cells and blocks the virus life cycle at the stage of assembly. Currently, LNF is under study in combination with ritonavir that is used as a pharmacokinetic enhancer (booster) [40]. Overall, LNF increases the therapeutic efficacy of Peg-IFNα [41]. Recently, in a phase-2 six-month study LNF achieved virologic responses even in a INF-free regimen, 7 of 7 (100%) patients treated with LNF + Ritonavir [42], but long-term therapies are required to achieve clinical control of HDV infection. The above-mentioned REP-2139 also shows activity against HDV. In an open-label, non-randomised, phase 2 trial, 12 HBV/HDV-coinfected patients received REP-2139 in combination with Peg-IFNα-2a. Overall, 11 patients became HDV-RNA negative during treatment and 9 remained negative at the end of treatment. Seven patients remained HDV-RNA negative by the end of 1 year follow-up [36]. In another phase-2 study evaluating 12 patients, treated initially with REP-2139 500 mg intra venous (IV) for 15 weeks, followed by REP-2139 250 mg IV in association with Peg-IFNα-2a weekly for 15 weeks, and Peg-IFNα-2a weekly for another 33 weeks, 7 (58%) patients were found to be HDV-RNA negative and 5 (42%) HBsAg negative at 24-week follow-up [43]. Ezetimibe (phase-2), a NTCP inhibitor, shows activity against HDV resulting in a ≥1 log reduction of HDV-RNA level in patients treated for 12 weeks [44]. Finally, GI-18000 is an immune response stimulator in preclinical phase of development (Table 1).

HBV/HDV antivirals' side effects

Antiviral drugs antagonizing HBV and HDV may cause systemic inflammation-related symptoms, especially during induction. Systemic inflammation sustained by pro-inflammatory cytokines (i.e. TNF-alpha or IFN I) can provoke and maintain headache, myalgia, fatigue, anorexia, and vomiting that are often responsible for the patients' drop-out [45, 46]. In particular, IFN alpha and its pegylated

Table 1. New drugs for HBV and HDV treatment.

Author [ref.]	Drug	Country	Study	N° Patients enrolled	Target	Duration	Outcome
Bazinet [43]	REP2139 + pegIFNalfa-2a	Mutlicentric: Canada, US, Moldova, France, Germany	Phase 2	12	CHD	63 weeks	7/12 (58%) SVR
Yurdaydin [42]	Lonarfanib + Ritonavir +/- pegIFNalfa	Turkey	Phase 2	33	CHD	24 weeks	21/33 (64%) 2 log drop in HDV RNA

CHD: Chronic Hepatitis Delta; IFN: Interferon; SVR: Sustained virologic response.

variant are associated with severe systemic inflammatory symptoms that gradually decrease during the maintenance. Currently, the modulating role of diet during antiviral therapies for HBV is limited to a non-hepato-toxic one, without considering the anti-inflammatory properties of foods [47], and chronobiology [48]. Conversely from other antivirals, IFN displays a severe burden of psychiatric and hematological side effects, capable of compromising both the overall patients' quality of life and therapy tolerability. In particular, bone marrow alterations (i.e. leukocytopenia) may expose patients to long-term autoimmune and/or infective sequelae [49, 50]. In healthy people the Hepatitis B vaccine can transitorily increase the amount of released IFN; instead in patients with autoimmunity, the Hepatitis B vaccine may trigger a flare [51, 52]. Other antivirals have a higher airway impairment, especially for upper airways that are frequently colonized and infected by different pathogens [53]. Thus, in patients with inflammatory comorbidities also involving airways, IFN should be preferred [54-58]; conversely in oncological patients under chemotherapy lamivudine is the first choice due to its scarce pro-emetic effect [59]. Among antivirals, only IFN is subcutaneously injected, and this practice is connected with several injection site side effects (i.e. itch, pain and erythema); interestingly entecavir also causes several polymorphic dermatological side effects [60].

IFN and IFN-inducing drugs may alter the solar tolerability due to their pro-erythematous effects, and hence patients under these therapies are more photosensitive and should use a sunscreen and sunglasses, especially during summer.

Also, antiviral drugs are contraindicated in patients undergoing NB-UVB and PUVA treatment since they decrease the minimal erythemal dose (MED) limiting the amount of radiation tolerated. At the same time, HBV-positive patients cannot undergo biologics due to the risk of latent infection reactivation and have to face the undertreatment due to the lack of solid evidence [61]. IFN and telbivudine are preferred in patients with nephropathies, whilst adefovir, entecavir, and tenofovir are used in the patient with neuropathies [45]. Patients with osteoporosis and osteomalacia should skip adefovir and tenofovir, but not lamivudine which increases only myopathy. Patients with concomitant thyroidopathies should avoid only IFN and diabetic decompensated patients had to be strictly monitored since all these drugs trigger lactic acidosis. A detailed summary of most common antivirals side effects is collected in Table 2. In general, patients with mild and transitory side effects should be treated symptomatically; otherwise, in patients with long-term symptoms, clinicians should consider HBV/HDV treatment switching. Furthermore, the separation of dose-dependent and dose-independent side effects remains important in patients with HBV/HDV.

CONCLUSION

Hepatitis B remains a great concern for public health worldwide because of its growing resistance to the currently used antivirals together with its

Table 2. Adverse effects of the currently used antiviral agents for HBV and HDV treatment.

	IFNα and PEG-IFNα	**LAMIVUDINE**	**ADEFOVIR**	**ENTECAVIR**	**TELBIVUDINE**	**TENOFOVIR**
GENERAL SIDE EFFECTS	Flu-like symptoms, fatigue, myalgia, arthralgias, headache, anorexia, nausea/ vomit, diarrhea, weight loss [18, 60, 62]	Upper respiratory tract infection, nasopharyngitis, headache, fatigue [45]	Pharyngitis, fatigue, headache, abdominal pain, flu-like symptoms, nausea [45]	Headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, dizziness, upper abdominal pain, nausea [45]	Upper respiratory tract infection, nasopharyngitis, headache and fatigue [45]	Headache, nasopharyngitis, back pain, nausea [45]
PSYCHIATRIC	**Common:** depression [18, 60, 63], insomnia, anxiety [60, 63], cognitive disturbances [63], **Rare:** mania, delirium, psychosis [63]					
NEUROLOGICAL	Consciousness impairment [62]	Neuropathy [45, 46], acute dystonia (rare) [45]			Peripheral neuropathy (patients treated with TBV and PEG-IFNα) [45, 46]	
SENSORY	Blurred vision, hearing impairment [60]					
SKIN	**Injection site reactions:** itching, inflammation, rare necrosis [18, 64] **Hair changes:** hair loss [18, 60, 62, 64, 65] eyebrow and eyelash trichomegaly porphyria cutanea tarda [64],			Cutaneous lesions: anaphylaxis, granulomatous, erythematous plaque, maculopapular, bullous [66]		

Table 2 continued..

	Others: herpes labialis[62], psoriasis, sarcoidosis, lichenoid eruptions[64], lupus erythematosus [64, 65], bullous pemphigoid [65]					
KIDNEY		Nephrotoxicity [18], Fanconi syndrome [46]	Nephrotoxicity [18, 45, 46, 53], Fanconi syndrome [45, 53]	Nephrotoxicity [18]		Nephrotoxicity: glomerular and tubular (more prominent in HIV patients) [18, 45, 46, 53]
BONE			Osteomalacia [53]			Bone mineral density loss [18, 45, 46, 53], osteomalacia [18, 46, 53] (more prominent in HIV patients)
MUSCLE		Myophaty [45, 46]			Myopathy [45, 46, 53]	
OTHERS	Lactic acidosis (if decompensated cirrhosis) [18]	Pancreatitis [45, 46], lactic acidosis (rare) [45, 53]	Pancreatitis [46], lactic acidosis [53]	Lactic acidosis (rare) [45, 53]	Lactic acidosis [45, 53]	Lactic acidosis [53]
LABORATORY FINDINGS	Leukopenia, neutropenia, thrombocytopenia [18, 60, 62], anemia [62], ALT flares [60], Thyroid dysfunction [60, 62]	ALT flares [45]	↓ GFR Hypophosphatemia [45]		↑CK [45, 53]	↓ GFR Hypophosphatemia [45]

↓: decrease; ↑: increase; ALT: alanine aminotransferase; HIV: Human Immunodeficiency Virus; GFR: glomerular filtration rate.

tumorigenic potential. Furthermore, HBV prevalence is the main risk factor for HDV infection. Chronic hepatitis Delta (CHD) is the most severe of chronic viral hepatitis, and although more than four decades have passed since the IFN introduction in the clinical practice it remains the cornerstone of antiviral therapy [67]. In compensated patients, PegIFN alfa is recommended for more than 48 weeks by the EASL [18], and for 12 months by the AASLD [17]; however, this treatment is not really effective, with about less than a fifth of patients getting a sustained virological response [68], contraindicated in many conditions (e.g. autoimmune diseases) and advanced liver disease [18], and with numerous adverse events described (Table 1).

AUTHOR CONTRIBUTIONS

This review was mainly written by Marco Fiore, Giovanni Damiani and Sebastiano Leone; Michela Del Simone, Silvia Sena, Dalila Bruno, Addolarata Masiello, and Francesca Martora collected the data; Marco Fiore, Sebastiano Leone, Giovanni Damiani, and Maria Caterina Pace supervised the writing of the paper; Conic RRZ critically revised the English Language; all authors approved the final version to be published.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare that are relevant to the content of this review.

REFERENCES

1. Coppola, N., Tonziello, G., Pisaturo, M., Messina, V., Guastafierro, S., Fiore, M., Iodice, V., Sagnelli, C., Stanzione, M., Capoluongo, N., Pasquale, G. and Sagnelli, E. J. 2011, Med. Virol., 83, 1909-1916.
2. Block, T. M., Gish, R., Guo, H., Mehta, A., Cuconati, A., Thomas London, W. and Guo, J.-T. 2013, Antiviral Res., 98, 27-34.
3. Stockdale, A. J., Kreuels, B., Henrion, M. Y. R., Giorgi, E., Kyomuhangi, I., de Martel, C., Hutin, Y. and Geretti, A. M. 2020, J. Hepatol., 73, 523-532.
4. (WHO), W.H.O. Global hepatitis report. Available online: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/ (accessed on June 1, 2021)
5. Sagnelli, E., Sagnelli, C., Pisaturo, M., Macera, M. and Coppola, N. 2014, World J. Gastroenterol., 20, 7635-7643.
6. Liaw, Y. F. and Chu, C. M. 2009, Lancet, 373, 582-592.
7. (WHO), W.H.O. Hepatitis B. Available online: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (accessed on June 1, 2021)
8. World Health, O. Hepatitis B vaccines: WHO position paper, July 2017 - Recommendations. Vaccine 2019, 37, 223-225.
9. Nelson, N. P., Easterbrook, P. J. and McMahon, B. J. 2016, Clin. Liver Dis., 20, 607-628.
10. Yurdaydin, C., Idilman, R., Bozkaya, H. and Bozdayi, A. M. 2010, J. Viral Hepat., 17, 749-756.
11. Suk-Fong Lok, A. 2019, Hepatol. Commun., 3, 8-19.
12. Yoo, J., Hann, H. W., Coben, R., Conn, M. and DiMarino, A. J. 2018, Diseases, 6.
13. Mason, S., Devincenzo, J. P., Toovey, S., Wu, J. Z. and Whitley, R. J. 2018, Antiviral Res., 158, 103-112.
14. Liu, Y., Corsa, A. C., Buti, M., Cathcart, A. L., Flaherty, J. F., Miller, M. D., Kitrinos, K. M., Marcellin, P. and Gane, E. J. 2017, J. Viral Hepat., 24, 68-74.
15. Tenney, D. J., Rose, R. E., Baldick, C. J., Pokornowski, K. A., Eggers, B. J., Fang, J., Wichroski, M. J., Xu, D., Yang, J., Wilber, R. B. and Colonno, R. J. 2009, Hepatology, 49, 1503-1514.
16. Miao, Z., Zhang, S., Ou, X., Li, S., Ma, Z., Wang, W., Peppelenbosch, M. P., Liu, J. and Pan, Q. J. 2020, Infect. Dis., 221, 1677-1687.
17. Terrault, N. A., Lok, A. S. F., McMahon, B. J., Chang, K. M., Hwang, J. P., Jonas, M. M., Brown, R. S. Jr., Bzowej, N. H. and Wong, J. B. 2018, Hepatology, 67, 1560-1599.
18. European Association for the Study of the, Liver. 2017, J. Hepatol., 67, 370-398.
19. Sarin, S. K., Kumar, M., Lau, G. K., Abbas, Z., Chan, H. L., Chen, C. J., Chen, D. S., Chen, H. L., Chen, P. J., Chien, R. N., Dokmeci, A. K., Gane, E., Hou, J. L., Jafri, W., Jia, J., Kim, J. H., Lai, C. L., Lee, H. C., Lim, S. G., Liu, C. J., Locarnini, S., Al Mahtab, M., Mohamed, R., Omata, M., Park, J.,

Piratvisuth, T., Sharma, B. C., Sollano, J., Wang, F. S., Wei, L., Yuen, M. F., Zheng, S. S. and Kao, J. H. 2016, Hepatol. Int., 10, 1-98.
20. Vittal, A. and Ghany, M. G. 2019,Clin. Liver Dis., 23, 417-432.
21. Farci, P., Mandas, A., Coiana, A., Lai, M. E., Desmet, V., Van Eyken, P., Gibo, Y., Caruso, L., Scaccabarozzi, S., Criscuolo, D., Ryff, J. C. and Balestrieriet, A. N. 1994, Engl. J. Med., 330, 88-94.
22. Farci, P., Roskams, T., Chessa, L., Peddis, G., Mazzoleni, A. P., Scioscia, R., Serra, G., Lai, M. E., Loy, M., Caruso, L., Desmet, V., Purcell, R. H. and Balestrieri, A. 2004, Gastroenterology, 126, 1740-1749.
23. Huang, D. Q. and Lim, S. G. 2020, Liver Int., 40(Suppl. 1), 5-14.
24. Yan, H., Zhong, G., Xu, G., He, W., Jing, Z., Gao, Z., Huang, Y., Qi, Y., Peng, B., Wang, H., Fu, L., Song, M., Chen, P., Gao, W., Ren, B., Sun, Y., Cai, T., Feng, X., Sui, J. and Li, W. 2012, Elife, 1.
25. Verrier, E. R., Schuster, C. and Baumert, T. F. 2017, J. Hepatol., 66, 677-679.
26. Bogomolov, P., Alexandrov, A., Voronkova, N., Macievich, M., Kokina, K., Petrachenkova, M., Lehr, T., Lempp, F. A., Wedemeyer, H., Haag, M., Schwab, M., Haefeli, W. E., Blank, A. and Urban, S. 2016, J. Hepatol., 65, 490-498.
27. Wedemeyer, H., Schöneweis, K., Bogomolov, P. O., Voronkova, N., Chulanov, V., Stepanova, T., Bremer, B., Allweiss, L., Dandri, M., Burhenne, J., Haefeli, W., Ciesek, S., Dittmer, U., Alexandrov, A. and Urban, S. 2019, J. Hepatol., 70, e81.
28. Flisiak, R., Jaroszewicz, J. and Lucejko, M. 2018, Expert Opin. Biol. Ther., 18, 609-617.
29. Gane, E., Locarnini, S., Lim, T.H., Strasser, S., Sievert, W., Cheng, W., Thompson, A., Given, B., Schluep, T., Hamilton, J., Biermer, M.,Kalmeijer R., Beumont, M., Lenz O., Cloherty, G., Ka-Ho Wong, D., Schwabe, C., Jackson, K., Ferrari, C., Lung Lai, C., Gish, R. G. and Yuen, M. F. 2020, J. Hepatol., 73, S20.
30. Lopatin, U. 2019, Clin. Liver Dis., 23, 535-555.
31. Gane, E., Lim, Y.-S., Tangkijvanich, P., O'Beirne, J., Lim, T. H., Bakardjiev, A., Ding, X., Connolly, L., Huang, S., Kim, J., Pang, P. and Yuen, R. M. F. 2020, J. Hepatol., 73, S50-S51.
32. Soriano, V., Barreiro, P., Cachay, E., Kottilil, S., Fernandez-Montero, J. V. and de Mendoza, C. 2020, Ther. Adv. Infect. Dis., 7.
33. Huang, Q., Cai, D., Yan, R., Li, L., Zong, Y., Guo, L., Mercier, A., Zhou, Y., Tang, A., Henne, K. and Colonno R. 2020, Antimicrob. Agents Chemother., 64.
34. Yuen, M. F., Agarwal, K., Gane, E. J., Schwabe, C., Ahn, S. H., Kim, D. J., Lim, Y. S., Cheng, W., Sievert, W., Visvanathan, K., Ruby, E., Liaw, S., Yan, R., Huang, Q., Colonno, R. and Lopatin, U. 2020, Lancet Gastroenterol. Hepatol., 5, 152-166.
35. Zoulim, F., Lenz, O., Vandenbossche, J. J., Talloen, W., Verbinnen, T., Moscalu, I., Streinu-Cercel, A., Bourgeois, S., Buti, M., Crespo, J., Manuel Pascasio, J., Sarrazin, C., Vanwolleghem, T., Shukla, U., Fry, J. and Yogaratnam, J. Z. 2020, Gastroenterology, 159, 521-533.e529.
36. Bazinet, M., Pantea, V., Placinta, G., Moscalu, I., Cebotarescu, V., Cojuhari, L., Jimbei, P., Iarovoi, L., Smesnoi, V., Musteata, T., Jucov, A., Dittmer, U., Krawczyk, A. and Vaillant, A. 2020, Gastroenterology, 158, 2180-2194.
37. Tanwandee, T., Chatsiricharoenkul, S., Thongsawat, S., Sukeepaisarnjaroen, W., Tangkijvanich, P., Komolmit, P., Avihingsanon, A., Piratvisuth, T., Sunthi, P., Mahasanprasert, T., Matkovits, T., Conover, M., Cobb, J., Canizares, C. and Sullivan-Bolyai, J. 2017, J. Hepatol., 66, S24-S25.
38. Sekiba, K., Otsuka, M., Ohno, M., Yamagami, M., Kishikawa, T., Suzuki, T., Ishibashi, R., Seimiya, T., Tanaka, E. and Koike, K. 2019, Cell. Mol. Gastroenterol. Hepatol., 7, 297-312.
39. Joly, S., Porcherot, M., Radreau, P., Vonderscher, J., André, P., Meldrum, E., Arold, G., Van de Wetering de Rooij, J., Staner, C., Laveille, C. and Scalfaro, P. 2017, J. Hepatol, 66, S690.

40. Yurdaydin, C., Keskin, O., Kalkan, C., Karakaya, F., Caliskan, A., Karatayli, E., Karatayli, S., Bozdayi, A. M., Koh, C., Heller, T., Idilman, R. and Glenn, J. S. 2018, Hepatology, 67, 1224-1236.
41. Caviglia, G. P. and Rizzetto, M. 2020, Clin. Microbiol. Infect., 26, 824-827.
42. Yurdaydin, C., Kalkan, C., Karakaya, F., Caliskan, A., Karatayli, S., Keskin, O., Idilman, R., Bozdayi, M., Koh, C., Heller, T. and Glenn, J. S. 2018, J. Hepatol., 68, S89.
43. Bazinet, M., Pântea, V., Cebotarescu, V., Cojuhari, L., Jimbei, P., Albrecht, J., Schmid, P., Le Gal, F., Gordien, E., Krawczyk, A., Mijočević, H., Karimzadeh, H., Roggendorf, M. and Vaillant, A. 2017, Lancet Gastroenterol. Hepatol., 2, 877-889.
44. Abbas, Z., Saad, M., Asim, M., Abbas, M. and Samejo, S. A. 2020, Turk. J. Gastroenterol., 31, 136-141.
45. Kayaaslan, B. and Guner, R. 2017, World J. Hepatol., 9, 227-241.
46. Khungar, V. and Han, S. H. 2010, Curr. Hepat. Rep., 9, 75-90.
47. Damiani, G., Bragazzi, N. L., McCormick, T. S., Pigatto, P. D. M., Leone, S., Pacifico, A., Tiodorovic, D., Di Franco, S., Alfieri, A. and Fiore, M. 2020, World J. Clin. Cases, 8, 1002-1012.
48. Barrea, L., Nappi, F., Di Somma, C., Savanelli, M. C., Falco, A., Balato, A., Balato, N. and Savastano, S. 2016, Int. J. Environ. Res. Public Health, 13.
49. Qi, W. Q., Zhang, Q., Wang, X., Xu, Y., Zhao, P., Guo, H. H., Zhou, C. Y., Sun, Y., Liu, L. and Wang, J. B. 2021, Neoplasma, 68, 200-207.
50. Damiani, G., Franchi, C., Pigatto, P., Altomare, A., Pacifico, A., Petrou, S., Leone, S., Pace, M. C. and Fiore, M. 2018, World J. Hepatol., 10, 329-336.
51. Watad, A., Bragazzi, N. L., McGonagle, D., Adawi, M., Bridgewood, C., Damiani, G., Alijotas-Reig, J., Esteve-Valverde, E., Quaresma, M., Amital, H. and Shoenfeld, Y. 2019, Clin. Immunol., 203, 1-8.
52. Arafa, A. and Mostafa, A. 2020, Australas. J. Dermatol., 61, 382-384.
53. Fung, J., Seto, W. K., Lai, C. L., Yuen, M. F. 2014, J. Gastroenterol. Hepatol., 29, 428-434.
54. Damiani, G., Della Valle, V., Iannone, M., Dini, V., Marzano, A. V. 2017, Ann. Rheum. Dis., 76, e25.
55. Santus, P., Rizzi, M., Radovanovic, D., Airoldi, A., Cristiano, A., Conic, R., Petrou, S., Pigatto, P. D. M., Bragazzi, N., Colombo, D., Goldust, M. and Damiani, G. 2018, Biomed Res. Int., 2018, 3140682.
56. Damiani, G., Pigatto, P. D. M., Marzano, A. V., Rizzi, M., Santus, P., Radovanovic, D., Loite, U., Torelli, L., Petrou, S., Sarzi-Puttini, P., Atzeni, F., Adawi, M., Bridgewood, C., Bragazzi, N. L., Watad, A., Malerba, M. 2019, Clin. Rheumatol., 38, 2541-2546.
57. Damiani, G., Radaeli, A., Olivini, A., Calvara-Pinton, P. and Malerba, M. 2016, Br. J. Dermatol., 175, 797-799.
58. Damiani, G., Pacifico, A., Rizzi, M., Santus, P., Bridgewood, C., Bragazzi, N. L., Adawi, M. and Watad, A. 2020, Clin. Rheumatol., 39, 2981-2988.
59. Tang, L. S. Y., Covert, E., Wilson, E. and Kottilil, S. 2018, JAMA 319, 1802-1813.
60. Yang, J. F., Kao, Y. H., Dai, C. Y., Huang, J. F., Hsieh, M. Y., Lin, Z. Y., Chen, S. C., Hsieh, M. Y., Wang, L. Y., Chuang, W. L. and Yu, M. L. 2010, Hepatol. Int., 4, 732-740.
61. Bonifati, C., Lora, V., Graceffa, D. and Nosotti, L. 2016, World J. Gastroenterol., 22, 6444-6455.
62. Abbas, Z., Khan, M. A., Salih, M. and Jafri, W. 2011, Cochrane Database Syst. Rev., 10.1002/14651858.CD006002.pub2, CD006002.
63. Kovacs, D., Kovacs, P., Eszlari, N., Gonda, X. and Juhasz, G. 2016, Curr. Opin. Pharmacol., 29, 97-103.
64. Mistry, N., Shapero, J. and Crawford, R. I. 2009, Can. J. Gastroenterol., 23, 677-683.
65. Grigorescu, I. and Dumitrascu, D. L. 2014, World J. Gastroenterol., 20, 15860-15866.
66. Temiz, S. A., Ozer, I., Ataseven, A. and Findik, S. 2019, Turk J. Gastroenterol., 30, 299-302.

67. Yurdaydin, C., Abbas, Z., Buti, M., Cornberg, M., Esteban, R., Etzion, O., Gane, E. J., Gish, R. G., Glenn, J. S., Hamid, S., Heller, T., Koh, C., Lampertico, P., Lurie, Y., Manns, M., Parana, R., Rizzetto, M., Urban, S. and Wedemeyer, H. 2019, J. Hepatol., 70, 1008-1015.
68. Loglio, A., Segato, S. and Lampertico, P. 2019, Expert Rev. Clin. Pharmacol., 12, 169-171.