Investigational drugs with dual activity against HBV and HIV (Review)

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Abstract. Chronic hepatitis B (CHB) and acquired immunodeficiency syndrome (AIDS) are global public health problems that pose a significant health burden. Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) coinfection is common, as these viruses have similar transmission routes, such as blood transmission, sexual transmission and mother-to-child transmission. Coinfection frequently leads to accelerated disease progression. For individuals coinfected with HIV/HBV, combination antiretroviral therapy containing dual anti-HBV drugs is recommended. Certain studies have also indicated the benefits of antiretroviral drugs with anti-HBV activity in patients with coinfection. A total of four Food and Drug Administration-approved HIV drugs also have anti-HBV activity; namely, emtricitabine, lamivudine, tenofovir disoproxil fumarate and tenofovir alafenamide, which are all nucleoside reverse transcriptase inhibitors. However, various issues, including drug resistance and side effects, limit their application. Therefore, it is necessary to develop more drugs with dual activity against HBV and HIV. The present review outlines the mechanisms, safety and efficacy of certain drugs that have been investigated for this purpose.

Contents

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Abbreviations: HBV, hepatitis B virus; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; TFV, tenofovir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; cART, combination ART; TLR-7, Toll-like receptor-7; PBMCs, peripheral blood mononuclear cells; NAs, nucleos(t)ide analogues; HCC, hepatocellular carcinoma; SIV, simian immunodeficiency virus; NK, natural killer; CYPs, cyclophilins; MMF, Mycophenolate mofetil; IMPDH, inosine monophosphate dehydrogenase; MPA, mycophenolic acid; dGTP, deoxyguanosine triphosphate; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors; TXL, tenofovir exalidex; HDP-TFV, Hexadecyloxypropyl-tenofovir

Key words: HIV, hepatitis B virus, coinfection, antiviral, dual activity drug, review

1. Introduction

Chronic hepatitis B (CHB) and acquired immunodeficiency syndrome (AIDS) are both serious public health problems and caused by viruses that have the same transmission paths, including mother-to-child, blood (including minor wounds of the skin and mucous membranes) and sexual contact. Due to their shared transmission routes, coinfections of hepatitis B virus (HBV) and HIV are common and ~5-20% of patients living with HIV infection worldwide are also infected with HBV (1). Compared with patients infected with only HBV, HIV/HBV-coinfected patients have a higher risk of developing end-stage liver disease and an overall higher mortality rate (2-4). Furthermore, the presence of HBV in HIV-positive patients is associated with a lower number of $CD4^+$ lymphocytes and a lower virologic response against HIV during treatment (5).

It is necessary for coinfected patients to start antiviral treatment as early as possible because as the degree of immunodeficiency worsens, the patient's response to HBV treatment regimens is reduced (6). Highly active antiretroviral therapy (HAART) is able to effectively promote immune system reconstitution (7). The World Health Organization (WHO)

recommends that patients living with HIV who are coinfected with HBV with severe chronic liver disease are required to initiate ART regardless of their WHO clinical stage and $CD4^+$ cell count (8) and Chinese guidelines also suggest that they need to start HAART if coinfected with HBV regardless of their $CD4^+$ cell count as early as possible (9). However, immune reconstitution syndrome secondary to HAART may cause hepatitis flares; therefore, HBV and HIV should be treated at the same time (7). Using one drug that is active against HBV is able to induce HIV resistance to nucleoside drugs; therefore, two anti-HBV drugs should be included in the treatment plan. For HIV/HBV coinfected individuals, combination ART (cART) with dual anti-HBV and anti-HIV antiretroviral activity is recommended (10). The treatment goals are to control HIV and HBV transmission, suppress viral replication and prevent drug resistance mutations in reverse transcriptase (4). The treatment duration for HBV in coinfected patients is indefinite due to the low response rates and the requirement for lifelong treatment for HIV (11). Thus, the drugs should be selected carefully and closely monitored during treatment to minimize the risk of HBV and HIV drug resistance.

Numerous studies have proven the importance of dual activity drugs for coinfection treatment. Using highly effective cART with dual activity is able to significantly reduce the risk of developing end-stage liver disease in HIV/HBV coinfected patients (12). Interruption of HIV medications with anti-HBV activity in HIV/HBV coinfected individuals may result in HBV reactivation and/or hepatitis (13). HIV mono-infected patients may be protected from HBV infection by using anti-HBV antiretroviral medications (14). However, only four Food and Drug Administration (FDA)-approved HIV drugs that have anti-HBV activity have been developed thus far, namely emtricitabine, lamivudine, tenofovir (TFV) disoproxil fumarate (TDF) and TFV alafenamide (TAF), all of which are nucleoside reverse transcriptase inhibitors (15). In a meta-analysis, the evidence for the relative effectiveness of these drugs in the treatment of HBV/HIV coinfection was insufficient (3). Considering the drug resistance of HBV and HIV and the side effects of the medications, the development of novel drugs with dual activity is urgent to ensure that there is a sufficient number of alternative drugs for treating HIV/HBV coinfection. Fortunately, antiretroviral drugs with dual activity for treating HBV and/or HIV are under different pre-clinical or clinical study stage. In the present review, the mechanisms, safety and effectiveness of drugs investigated for HIV/HBV coinfection are provided.

2. Immunomodulators

GS-9620. Toll-like receptor-7 (TLR-7) has a vital role in the innate immune response against pathogens. GS-9620, also called vesatolimod, was developed by Gilead and is a potent, selective and orally active small-molecule agonist of TLR-7. GS-9620 is able to activate T cells and natural killer (NK) cells, inducing immune activation. Furthermore, GS-9620 is capable of increasing the plasma levels of various cytokines and the expression levels of associated genes, such as IFNα and IFN-stimulated genes (16). CHB is characterized by persistently low innate and adaptive immune responses. Therefore, the TLR7 agonist GS-9620 may have the potential for improving anti-HBV immunity. Certain studies have indicated that GS-9620 is able to sustainably suppress viral DNA and antigens in the sera of woodchuck and chimpanzee models of CHB (17,18). The mean maximum reduction in viral DNA was 2.2 logs and reductions of >1 log persisted for months in HBV-infected chimpanzees treated with GS-9620 (18). In another study, GS-9620 reduced the levels of HBV DNA, RNA and antigens *in vitro* in HBV infection models (19). Furthermore, GS-9620 administration reduced covalently closed circular (ccc)DNA levels and the incidence of hepatocellular carcinoma (HCC) in woodchucks with chronic woodchuck hepatitis virus infection (17). Clinical research on GS-9620 in patients with CHB is preliminary. Oral administration of GS-9620 at 1-, 2- or 4-mg doses did not cause any significant decrease in hepatitis B surface antigen (HBsAg) in patients with CHB who were not taking any oral antivirals or who were virally suppressed by oral antiviral treatment, which may be due to differences in dose administration and/or concentration and species-specific effects of the therapy in the animal and human CHB models. However, GS-9620 has been indicated to be safe and well-tolerated in patients with CHB (20-22).

HIV-1 infection remains incurable due to a persistent viral reservoir, requiring the administration of antiretroviral drugs throughout life. Long-lived memory $CD4^+$ T cells serve as the primary reservoir of latent HIV. Interrupted HIV treatment may result in viral reactivation. The latent reservoir in resting $CD4^+$ T cells is considered to be the major obstacle to HIV treatment. Toll-like receptor agonists are able to reverse HIV-1 latency (23), induce latent HIV expression and promote the immune system to recognize and eliminate infected cells. Tsai *et al* (24) and Sloan *et al* (25) indicated that GS-9620 has the ability to activate HIV expression *ex vivo* in peripheral blood mononuclear cells (PBMCs) isolated from HIV-infected patients with suppressive cART. Furthermore, GS-9620 is capable of augmenting the ability to kill HIV-infected cells through enhanced HIV-specific cellular cytotoxicity and anti-HIV antibody-mediated immunity. Treatment of PBMCs with GS-9620 induced a concentration-dependent increase in HIV-specific $CD8^+$ T-cell activation (26). In addition, treatment with GS-9620 significantly reduced the viral reservoir in simian immunodeficiency virus (SIV)-infected rhesus monkeys (27). Borducchi *et al* (28) reported that the V3 glycan-dependent broadly neutralizing antibody, PGT121, combined with GS-9620 delayed viral rebound following ART discontinuation in simian HIV-infected monkeys. Of note, no serious adverse events were observed in virologically suppressed HIV-1-infected adults when the doses of GS-9620 were increased in a phase 1b study (29). Overall, GS-9620 may be a candidate drug with dual effects caused by the regulation or activation of innate and adaptive immunity.

IFN. IFNs have potent antiviral effects. They exert antiviral activity by regulating the immune response and upregulating the expression of antiviral genes. IFNα is an FDA-approved medicine currently used to treat HBV and HCV infections due to its robust antiviral activity. Pegylated IFN, usually called Peg-IFN, is a chemically modified form of standard IFN.

Compared with standard IFN, Peg-IFN has a longer half-life and stays in the body for a longer duration. Peg-IFNα is available in two forms, peg-IFNα-2a and-2b, with the commercial names Pegasys and PegIntron, respectively.

Compared with that of nucleos(t)ide analogs (NAs), treatment with Peg-IFNα has the advantages of limited treatment duration, a higher rate of HBeAg and HBsAg seroconversion, a higher chance of sustained off-treatment virological response and lack of resistance. Furthermore, treatment with Peg-IFNα has a lower HBV-associated HCC incidence than NAs in HBV-infected patients (30). However, Peg-IFNα has been associated with severe adverse events, has low efficacy of viral suppression and is administered by subcutaneous injection, which are disadvantages. IFN therapy is contraindicated in patients with decompensated cirrhosis, pregnancy, heart failure, chronic obstructive pulmonary disease and psychosis. Thus, pegylated IFN must be carefully selected according to the patient's condition.

Furthermore, IFNs have anti-HIV activity (31-39). According to Frissen *et al* (37), high-dose IFNα-2a had potent anti-HIV activity. Asmuth *et al* (35) reported that pegylated IFNα-2a treatment reduced the viral load in untreated HIV-infected patients without HCV infection. Pegylated IFNα-2a is also useful in patients with multiple resistance-associated mutations and who are resistant to most antiretroviral medications (40). Furthermore, several studies suggested that treatment with IFNα may diminish the HIV reservoir size (31-33). However, the effect of IFN on HIV remains controversial due to potential deleterious effects during later stages of HIV infection. Sandler *et al* (41) suggested that continuous IFNα-2a therapy may lead to IFN desensitization and antiviral gene downregulation, thereby increasing the SIV reservoir size and accelerating CD4 cell depletion. IFNα levels were positively correlated with viral load and negatively correlated with the $CD4^+$ T-cell count in chronic HIV infection (42,43). Cheng *et al* (44) confirmed that blocking the sustained elevations in IFN-I signaling enhanced immune recovery and reduced HIV-1 reservoirs. However, another study indicated that the reduction in $CD4^+$ cells may be due to the HIV-infected cells being more vulnerable to IFNα-mediated attacks, resulting in a decrease in HIV DNA (39).

In summary, the interaction between HIV and type I IFNs is complex and the effects of IFNs on HIV remain uncertain; however, they may still be part of an effective strategy for eradicating the virus. The concentration and regimen of IFN should be carefully selected to ensure that they trigger the appropriate antiviral response. Thus, the benefit of IFN treatment outcomes may depend on the stage of HIV infection and the patient's immune status.

IL-15. IL-15, a 14- to 15-kDa cytokine, is able to eliminate viruses in infected cells by enhancing innate and adaptive immunity through inducing the activation and proliferation of T and NK cells. Among HIV-infected patients who have received structured treatment interruption (STI), HIV replication control was associated with sustained IL-15 levels (45). IL-15 has been proven to attenuate the impairment of NK cells in chronic HBV carriers (46). IL-15 therapy is also able to augment NK-cell function in virus-suppressed HIV-positive individuals on ART, and IL-15-stimulated NK cells may eliminate latently HIV-infected cells exposed to the histone deacetylase inhibitor vorinostat (a latency reversal agent) (47). IL-15 and ALT-803 (an IL-15 superagonist, also known as N-803) drove virus transcripts in latently infected CD4 T cells *in vitro* to be recognized by autologous HIV-specific CD8 T-cells, suggesting their roles as latency-reversing agents (48). In ART-suppressed, SIV-infected macaques and HIV-infected humanized mice, ALT-803 combined with CD8 lymphocyte depletion induced a sustained and robust reversal of latency (49). Another study suggested that the administration of ALT-803 temporarily inhibited viral replication in SIV-infected animals without ART (50). Walter *et al* (51) revealed that high levels of IL-15 in breast milk prevented postnatal HIV transmission. In addition, IL-15 has potential as an immune adjuvant. Coadministration of HIV vaccine vectors and vaccinia viruses expressing IL-15 contributed to the robust $CD8^+$ T-cell responses (52). However, IL-15 may have a deleterious role in HIV infection, particularly in the acute phase. IL-15 is able to increase the viral set point and accelerate disease progression (53). It abrogated the decrease in viral load induced by vaccines in SIV-infected macaques (54). IL-15 was significantly associated with HIV viremia and negatively correlated with the CD4+ cell count in HIV-1 infected patients with viral loads of >100,000 copies/ml, which was associated with IL-15-induced immune activation (55). In addition, IL-15 may cause tissue damage due to its strong proinflammatory properties and T cell-mediated alveolitis induced by IL-15 has been confirmed in patients with AIDS (56).

Only a small number of studies have demonstrated the inhibitory effect of IL-15 on HBV replication (57,58). In IL-15-treated HBV transgenic mice, reduced viral loads in the serum and undetectable HBV DNA intermediates in the liver were observed (58). Hydrodynamically injecting the plasmid pLIVE-IL-15, which expresses IL-15, into C57BL/6 mice reduced serum HBsAg and hepatitis B e antigen (HBeAg) titers and liver HBV DNA levels in an IFN-β-dependent manner (57). According to the results of certain studies (57,58), IL-15 may have therapeutic potential to inhibit HBV replication *in vivo*, but sufficient evidence supporting its effectiveness in humans is lacking.

Mycophenolate mofetil (MMF). MMF is an immunosuppressant that may be used as a prodrug of the active metabolite of mycophenolic acid to increase the bioavailability of mycophenolic acid. MMF is able to selectively and reversibly inhibit the type II isoform of inosine monophosphate dehydrogenase (IMPDH) in T and B lymphocytes and block the conversion of inosine monophosphate to guanosine monophosphate in the *de novo* synthetic pathway of the guanine purine (59). MMF is hydrolyzed to mycophenolic acid (MPA) *in vivo* and these two compounds have the same immune activity. Suppressing IMPDH in lymphocytes may cause guanosine triphosphate (GTP) and deoxyGTP (dGTP) depletion (60). Furthermore, inhibition of IMPDH activity may block T-lymphocyte proliferation (61) and increase the apoptosis rate of activated T lymphocytes (62). MMF exerts cytostatic effects and potential antiviral effects by depleting GTP and dGTP pools (63), and RNA and DNA synthesis require GTP or dGTP as substrates (64). MMF may be used as an adjuvant

for HIV-1 infection treatment and exerts an anti-HIV effect through the following three mechanisms: i) Depletion of substrates required for reverse transcriptase; ii) depletion of the activated $CD4^+$ T-lymphocyte pools and limitation of the availability of HIV-targeted cells (60); and iii) inhibition of syncytium formation by reducing the amount of gp120, which is a glycoprotein protruding from the outer surface of the HIV virion that has a molecular weight of 120 (64).

Numerous studies have demonstrated that MMF has activity against HIV *in vivo* and *in vitro* (63,65-69). Treatment of patients with acute HIV-1 infection with antiretroviral therapy (comprised of 5 drugs) combined with MMF (2 g/d) decreased the HIV-1 RNA load significantly and rendered HIV-1 antibody undetectable, but the RNA load rebounded when the treatment was stopped (70). In addition, adding MMF to HAART for HIV-1-infected patients reduced the number of latently infected $CD4^+$ T cells (69). A phase II study (NCT03262441) to determine whether administering MMF treatment for >22 months is able to reduce the reservoirs is currently ongoing. García *et al* (63) indicated that the combination of MMF with HAART delayed viral load rebound and MMF alone enhanced the control of viral replication when lymphocyte proliferation was suppressed. Furthermore, MMF is able to improve the activity of antiretroviral drugs in a dose-dependent manner (67,71,72). Coadministration of abacavir (a guanosine analog inhibitor) and MPA enhanced the anti-HIV effect of abacavir in both stimulated PBMC and monocyte-derived macrophages (60) and reduced the plasma levels of HIV RNA (73).

Similarly, MMF/MPA is able to theoretically inhibit HBV replication. MPA at a concentration of 10 μg/ml reduced the secretion of HBsAg and HBV DNA without inducing cytotoxicity, and HBV cccDNA and mRNA were undetectable (74). It is safe to use lamivudine and MMF prophylactically in renal transplant recipients with CHB who did not receive any antiviral therapy prior to transplantation (75). In a mouse model with hydrodynamic injection, MMF reduced the serum HBsAg and HBV DNA levels (76). In another study, MPA inhibited HBsAg and HBeAg expression, as well as HBV DNA replication *in vitro* in a dose-dependent manner (77). Furthermore, MMF enhanced the anti-HBV activity of guanine- and diaminopurine-based nucleos(t)ide analogs such as lobucavir and entecavir, probably by reducing the competing natural substrate dGTP (78,79). Thus, MMF appears to have an inhibitory effect on HBV replication. However, in certain studies, this inhibitory activity was not detected. MMF has the ability to inhibit hepatic NK-cell proliferation and activity *in vivo*, where NK cells have a critical role in the defense against HBV infection. A study suggested that MMF was not beneficial in suppressing HBV replication after liver transplantation in lamivudine-resistant patients (80). Treatment with MMF alone may stimulate virus replication with glomerulonephritis in patients who are HBV carriers but had not received antiviral treatment (81). Pyrimidine synthesis inhibitor (leflunomide, FK778) and MPA increased the risk of HBV replication in cell culture models (82). In summary, MPA may both inhibit and stimulate the proliferation of HBV. Based on this contradictory phenomenon, Pan *et al* (83) evaluated the effects of MPA in HepG2.2.15 cells and indicated that a low dose (1 μg/ml) of MPA increased the HBV titers, while a high dose (5 and 10 μg/ml) of MPA decreased HBV titers. However, all three doses of MPA significantly increased HBsAg expression, which was consistent with previous results (84); thus, it may be assumed that MPA has proviral effects.

MMF appears to be safe and the common side effects of MMF are usually mild (85). MMF, as an immunosuppressant, has not been approved for treating HIV or HBV infection, as the evidence is insufficient. More clinical trials are required to confirm its antiviral activity. However, it is still expected to become an adjuvant treatment for HIV.

3. Monoclonal antibodies

Cemiplimab. Programmed cell death receptor 1 (PD-1) is an immune checkpoint molecule that is necessary to maintain immune homeostasis upon binding to its ligands, programmed cell death ligand 1 (PD-L1) and ligand 2 (PD-L2). The PD-1/PD-L1 axis has a crucial role in viral infection and is upregulated in CHB and chronic HIV infections, where it may maintain chronic infection by attenuating the antiviral immune responses mediated by T cells or NK cells (86,87). PD-1 is intensely and extensively expressed during chronic infection. As mentioned above, even after receiving long-term cART, the latent reservoir in HIV-positive patients remains in resting $CD4^+$ cells expressing PD-1 (88). By establishing an HIV latency model *in vitro*, Evans *et al* (89) demonstrated that PD-1^{high} $CD4^+$ memory T cells had high levels of latency and that blocking PD-1 prior to infection reduced the incidence of latency, suggesting that PD-1 may help to establish and maintain latent HIV infection. PD-1/PD-L1 blockade enhanced viral-specific T-cell function, increased memory B-cell proliferation (90,91) and restored or enhanced host immune functions. Blocking the PD-1/PD-L1 pathway may contribute to treating chronic infections. Several studies have indicated that blocking PD-1 has an effect on HBV/SIV (92-95) and promotes latency reversal (89,96). In addition, PD-1, as an important immunosuppressive agent, may help to prevent severe liver damage and blocking the PD-1/PD-L1 axis may cause liver cell destruction and HBV reactivation (97). One study demonstrated that during anti-PD-1 treatment, certain patients with resolved HBV infection developed HBV reactivation (98). Therefore, blocking PD-1/PD-L1 may have a certain value in treating HBV/HIV infection, but the HBV reactivation risk cannot be ignored.

Cemiplimab (REGN2810) is a high-affinity and hinge-stabilized IgG4 monoclonal antibody against cell surface PD-1 (99), which was developed by Regeneron Pharmaceuticals in collaboration with Sanofi. As previously mentioned, the antiviral effect of certain PD-1/PD-L1 inhibitors has been confirmed in HIV/SIV and HBV models; therefore, it is speculated that cemiplimab may have a similar impact and potential to treat HIV/HBV coinfection. Currently, two phase I/II studies are underway to evaluate the safety and immunotherapeutic activity of cemiplimab in patients infected with HIV-1 or HBV on suppressive antiviral therapy [NCT03787095 (100) and NCT04046107 (101)].

Pembrolizumab. Similar to the above, pembrolizumab (Keytruda) is an IgG4 monoclonal antibody targeted to

PD-1. A phase I study indicated that pembrolizumab was safe in the treatment of different types of cancer in patients living with HIV and one participant experienced persistent low-level HIV viremia (<400 copies/ml) (102). Patients with metastatic melanoma treated with pembrolizumab remained safe in the context of their HBV infection (103); thus, pembrolizumab may be used to treat HBV infection in theory. However, a 51-year-old male patient diagnosed with stage IV lung adenocarcinoma developed reactivation of HBV when treated with pembrolizumab (104). A phase I study to detect the safety of a single dose of pembrolizumab in HIV-positive patients without cancer is currently underway (NCT03239899) (105). However, the safety and efficacy of PD-1 inhibitors in HIV/HBV coinfected patients remain uncertain. The evidence is still insufficient to indicate that treating HBV- or HIV-positive patients in the absence of tumors with PD-1/PD-L1 inhibitors is effective, as patients with HBV or HIV infection have traditionally been excluded from clinical trials due to a theoretical risk of immune reconstitution inflammatory syndrome (106). Although a small number of studies (104,107) on PD-1 inhibitors in HBV mono-infection are available, suggesting that they may have a proviral effect, these inhibitors enhance host immune functions and are a promising immunotherapy for HIV/AIDS (108). Targeting the PD1/PD-L1 pathway may be used as a therapeutic strategy to improve immune function and target the viral reservoir (109). Combination therapy may be a more promising treatment strategy. For instance, IL-15 combined with anti-PD-L1 antibody is able to enhance HIV-specific $CD8^+$-cell function (110).

4. Nucleoside/nucleotide reverse transcriptase inhibitors

TFV, a nucleotide (nucleoside monophosphate) analogue reverse transcriptase inhibitor, was originally described in 1993 (111) and was approved for clinical use in its oral prodrug form, such as TDF and TAF. TDF was the first selected for clinical development and was ultimately approved by the FDA for the treatment of HIV and HBV in 2001 and 2008, respectively (112). TAF was approved by the FDA in 2016 for treating HBV, which has higher safety than TDF. CMX157, also known as Hexadecyloxypropyl-TFV and TFV exalidex (TXL), is a novel lipid conjugate prodrug of TFV. It is the strategic collaboration project achieved by Contravir and Chemirex in 2014. It is effectively targeted to the liver and has higher antiviral activity and lower toxicity in the bone and kidney than TFV. CMX157 is considered to be an effective drug for treating HBV and HIV infection (113-118). The antiviral activity of CMX157 against HIV and HBV was 260-fold and 4.5-fold that of TFV *in vitro*, respectively (116). Furthermore, CMX157 is also effective in nucleoside/nucleotide-resistant HIV (115). In completed clinical trials, CMX157 was indicated to be safe and tolerable in healthy subjects and patients with HBV [NCT01080820 (119), NCT02710604 (120) and NCT02585440 (121)]. However, the agreement between Contravir and Chemirex was terminated in 2019. Whether Chemirex will continue to develop CMX157 is unclear (122). Considering that CMX157 has potent antiviral activity in HBV and HIV infection and it is still considered to be a promising drug. In view of its strong antiviral activity and low toxicity, it would be beneficial if Chemirex were able continue to develop CMX157.

5. Cyclophilins inhibitors

Cyclophilins (CYPs) belong to a protein family with peptidylprolyl isomerase activity; they promote protein folding and have essential roles in various biological processes. Among these proteins, CyPA is critical to HIV-1 and HBV virus replication (123,124). Certain studies indicated that CYP inhibitors interfere with HBV and HIV replication (125,126). CRV431 (formerly CPI-431-32) is a cyclophilin inhibitor that targets CypA and it has been demonstrated to possess broad-spectrum antiviral activity against HIV, HBV, HDV and HCV by disrupting the interactions between CypA and viral proteins (123). It blocks the interaction between CypA and the HIV-1 capsid to inhibit HIV replication. Furthermore, it also has efficacy against drug-resistant HIV-1 (127).

In addition, CRV431 is able to reduce multiple HBV infection markers, including DNA, HBsAg and HBeAg, by blocking the interaction between HBV X protein or HBsAg and CypA or by inhibiting viral entry, which relies on the vital receptor sodium taurocholate cotransporting polypeptide (128,129). CRV431 reduced the level of serum HBsAg and liver HBV DNA in transgenic mice in a dose-dependent manner, and it was also indicated that low-dose CRV431 (10 mg/kg/d) combined with the TFV prodrug TXL resulted in an additive inhibitory effect (130). A clinical trial to assess the safety, tolerability and pharmacokinetics of CRV431 in patients with CHB is currently ongoing [National Clinical Trial (NCT) identifier no. NCT03596697] (131).

A study demonstrated that CRV431 is metabolized mainly by the cytochrome P450 enzyme (124), while other nucleotide drugs are metabolized predominantly by the kidneys. Therefore, it was speculated that the potential drug-drug interaction between CRV431 and nucleotide drugs may be minimal. To date, CRV431 has demonstrated an excellent safety profile in all animal and clinical studies. Furthermore, CRV431 has antisteatosis, antiinflammatory, antifibrotic and antitumor activities (132). Therefore, CRV431 is a bright prospect in the treatment of liver diseases and serves as a promising drug for the treatment of liver disease and HIV-1 infection.

6. Conclusions

At present, there is a large number of HIV/HBV coinfected patients worldwide and it continues to increase. Coinfection of HBV and HIV is able to accelerate disease progression and may severely impact the health of patients. At present, it is recommended that coinfected patients use drugs with dual antiviral effects. However, there are several reasons to limit the applications of these drugs. Liver enzyme flares may be caused by drug resistance during HAART. Due to the genetic variability of HBV, certain HBV genotypes may naturally have lower sensitivity or resistance to certain anti-HBV drugs. For instance, genotype E exhibited a natural resistance to certain HBV medicines and HBC has a reduced sensitivity to IFNα (133). In addition, HBV may have cross-resistance to different drugs, such as those caused by lamivudine-induced resistance mutations, after several years of treatment and resistance to emtricitabine, as the two drugs have a similar

structure (134). Furthermore, treatment choices for HBV infection are limited by drug resistance to HIV. However, drugs with dual activity are able to prevent HBV and HIV reverse-transcriptase resistance mutations associated with drug resistance. In addition, renal function is a factor that requires to be considered when choosing drugs, particularly TDF/TAF, which have limitations for patients with renal insufficiency. Consequently, it is necessary to develop more drugs with dual activity. First, considering the rapid mutation rate of HBV and the frequent resistance of certain antiviral drugs, novel drugs with dual activity must be developed to address this problem. In addition, novel antiviral drugs may overcome the limitations caused by renal insufficiency and other side effects. Immune dysfunction in patients infected with HBV or HIV rapidly decreases the ability to control viral replication. Therefore, immunomodulators acting on the immune system are promising for the treatment of these two viruses. The potential of NRTIs and monoclonal antibodies for treating HBV and HIV is considerable. However, certain drugs are double-edged swords. Understanding the host's immune status and disease progression is essential for drug management. To date, most of dual-effect drugs are not available to the increasing number of coinfected individuals due to the limitations of drug resistance or toxicity, and the development of dual-activity drugs remains particularly urgent. In the present review, certain dual-activity drugs that are at the laboratory investigation stage were presented, but evidence to support their activity against HBV and HIV is limited and more clinical trials are required to prove the dual activity of these drugs.

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Authors' contributions

CS and CD contributed to the planning and design of the study. SS was responsible for the collection of references and writing of the manuscript. QY, YS and YF contributed to manuscript modification. All authors contributed to drafting the manuscript and interpretation of results. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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