Specific Medications for Chronic Viral Hepatitis

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Key Concepts

- Despite the vaccination policies and the effectiveness of nucleos(t)ide analogues (NAs) and interferon (IFN), the eradication of HBV still represents an unmet goal.
- The goal of new HBV treatments is a combination therapy, targeting multiple pathways of the virus and restoring immune response.
- Direct-acting antivirals (DAAs) opened a new era in HCV therapeutic management, achieving the goal of obtaining sustained virologic response in most patients with limited adverse effects.
- New techniques for testing and diagnosis and global access to expensive therapies represent future goals in HCV therapy.

53.1 Introduction

Infections caused by hepatitis viruses will probably increase at least until 2020 and represent one of the major causes of the development of chronic liver diseases, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [1]. Although showing the same hepatotropism, hepatitis viruses can be divided into five different families, according to their biological features, i.e. hepatitis A (HAV) and hepatitis E (HEV) viruses, causing almost exclusively acute self-limiting infections; hepatitis B (HBV) and hepatitis C (HCV) viruses, which are frequently causing chronic infections, and finally hepatitis D virus (HDV), a satellite virus whose replication depends on HBV presence. HAV and HEV infections do not cause chronic liver disease and are rarely fatal [2]. Although the majority of the hepatic diseases associated with HBV, HCV and HDV are chronic infections, the acute infections due to these viruses can be severe, and occasionally fulminant. According to the World Health Organization (WHO), HCV causes about 130 million cases of chronic infection and HBV about 240 millions, 15–20 millions of which due to HBV-HDV co-infection [3].

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53.2 Hepatitis B Virus (HBV) Infection

Chronic HBV infection represents a global health concern due to its still significant morbidity and mortality [4]. Despite the vaccination policies adopted in the last three decades, leading to a slight decrease of the global prevalence from 4.2% to 3.7%, the absolute number of chronically infected patients has grown from 223 million in 1990 to 240 million in 2005. In the United States, it has been estimated that 730,000 US residents may have chronic HBV infection, and this number can probably rise to about 2.2 million if high prevalence groups deriving from immigration from endemic countries are included [5].

Chronic HBV infection can be classified into five phases:

(I) HBeAg-positive chronic infection or immune tolerant phase
(II) HBeAg-positive chronic hepatitis
(III) HBeAg-negative chronic infection or 'inactive carrier' phase
(IV) HBeAg-negative chronic hepatitis
(V) HBsAg-negative phase.

The HBeAg-positive chronic infection is characterized by very high levels of HBV DNA (usually over 20,000 IU/mL), presence of HBeAg and persistently normal alanine aminotransferase (ALT) levels, which are increased in HBeAg-positive chronic hepatitis, as a marker of active hepatic inflammation.

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In HBeAg-negative chronic infection, patients usually show absent HBeAg, normal ALT, and undetectable or low levels of HBV DNA, generally below 2000 IU/mL. ALT values increase in HBeAg-negative chronic hepatitis, with liver necroinflammation and fibrosis. The HBsAg-negative phase, also known as "occult HBV infection", is characterized by absence of HBsAg and presence of anti-HBcAg antibodies, with or without detectable anti-HBsAg antibodies. It should be noticed that the evolution of chronic infection does not necessarily pass through every phase of the disease and the immune responses to each phase have not been fully characterized. However, the above reported classification of chronic HBV infection can be useful for finding more appropriate pharmacological treatments. Since the chronic infection is associated with an increased risk of developing cirrhosis and HCC, drug therapy is focused on improvement of survival and quality of life and also on prevention of disease progression, and consequently HCC development. The primary goal of current treatment strategies is the long-term suppression of HBV replication, although HBsAg loss represents a good surrogate end-point.

53.2.1 Treatment Strategies for HBV

Currently, two classes of drugs are approved for the treatment of chronic HBV infection: nucleos(t)ide analogues (NAs) and interferon (IFN) and its derivatives.

Although these drugs are effective in both suppressing viral replication and reducing hepatic inflammation, the eradication of HBV still represents an unmet goal. Generally, IFN therapy has a limited duration, whereas nucleos(t)ide analogues often need a life-long administration. This prolonged treatment is associated with a high risks of adverse reactions, drug resistance, nonadherence, and elevated cost. Nevertheless, the gold standard treatment is the long-term administration of a potent nucleos(t)ide analogue with high barrier to resistance, such as entecavir, tenofovir disoproxil or tenofovir alafenamide. However, in mild-to-moderate chronic HBV hepatitis, IFN treatment can also be considered. Since HCC remains the major concern for treated chronic patients, therapy response, adherence and risk of disease progression should be monitored. It should be noted that most current literature focuses only on the immune active phases of chronic HBV infection and, as a consequence, the therapy choice in both common and challenging clinical settings is based on indirect evidence and should consider individual patient preference and available resources.

53.2.1.1 Interferon (IFN)

Two formulations (standard and pegylated) of interferon (IFN and PegIFN-α) are available; PegIFN-α is generally better tolerated. In chronic HBV patients, IFN treatment produces the loss of HBV DNA and HBeAg and the development of anti-HBe antibody, together with an improvement of the biochemical and histological parameters of the liver. To achieve a lasting response and a long-term immunological control, PegIFN-α is used at moderate-to-high doses (5 or 10 MU/day) and with a limited duration treatment (typically a 4–6 weeks-course). The two main drawbacks of PegIFN-α are the high variability of response and the unfavorable safety profile, so that a significant number of patients are ineligible or unwilling to use this drug [6].

The prediction of individual responses can be assessed on the basis of several patient characteristics, such as disease activity, HBV genotype, stage of the disease, as well as levels of HBV DNA, HBsAg and HBeAg status [6]. Following these indications, PegIFN-α can be early discontinued in patients with a low probability of long-term response.

Theoretically, a combined therapy with NAs and PegIFN-α may provide advantages due to the synergistic antiviral effects of the two drugs [6–8]. However, evidence of the superiority of such an approach is lacking, and many questions regarding patient selection, timing and duration of the combination strategy are still unresolved. For these reasons, the combined therapy with NAs and PegIFN-α is not generally recommended.

53.2.1.2 Nucleos(t)ide Analogues (NAs)

Five NAs are approved for chronic HBV treatment: lamivudine, adefovir, entecavir, telbivudine and tenofovir (Fig. 53.1). These compounds can be classified into two classes: those having a low barrier (lamivudine, adefovir dipivoxil, telbivudine) and those with high barrier to HBV resistance (entecavir, tenofovir) [5, 6].

Usually, the NAs with high barrier to resistance (i.e., entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide) are used as a first-line choice, since, besides a low risk of drug resistance, they have a desirable safety profile and a potent long-term antiviral activity leading to undetectable HBV DNA levels in the majority of adherent patients [5, 6]. For these reasons, these compounds can be safely used in all HBV infected patients, representing the only treatment option for several patient subgroups (decompensated liver disease, liver transplants, extrahepatic manifestations, or severe chronic HBV exacerbation) [5, 9]. Moreover, NAs are successfully used to prevent HBV reactivation in patients under immunosuppression. Common adverse reactions of entecavir include headache, fatigue, dizziness, and nausea. Lactic acidosis and hepatomegaly with steatosis are possible complications for decompensated cirrhotic patients (Child-Pugh B and C). The main adverse effects of tenofovir are impairment of renal function, with renal tubular dysfunction (Fanconi syndrome), and decreased bone mineral density. Despite the high antiviral efficacy of entecavir and tenofovir, a

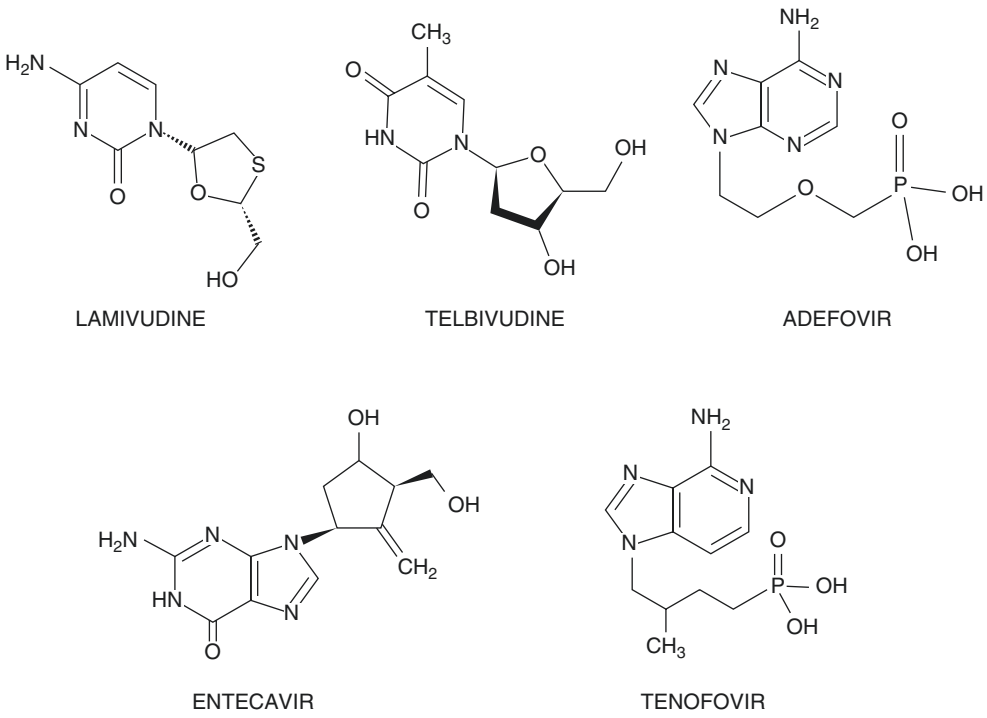

Fig. 53.1 NAs used in chronic HBV treatment

persistent viremia can be observed in some patients, particularly among HBeAg-positive ones with high baseline serum HBV DNA. Whether the association of a second antiviral agent increases the efficacy in patients with persistent viremia has not yet been tested.

The main characteristics (posology, pharmacokinetic profiles and possible drug-drug interactions) of the five NAs approved for HBV treatment are listed in Table 53.1.

53.2.1.3 HBV in Pregnancy

One of the major risk factors of chronic HBV infection is the perinatal or mother-to-child transmission (MTCT) of HBV in many high-prevalence areas [10]. In the absence of prophylaxis, MTCT may occur in up to 90% of HBsAg-positive and HBeAg-positive mothers. However, the administration of antiviral drugs during pregnancy is controversial, and precise guidelines on the risk-benefit balance are still unavailable. Although the highest risk of MTCT occurs during the immune tolerant phase, the benefit of antiviral therapy in preventing MTCT in this phase still awaits demonstration. Moreover, women in the immune active phase who have compensated liver disease can postpone antiviral treatment until delivery [10]. Additionally, it has been demonstrated that HBV infection can be prevented in approximately 90% of infants with post-delivery neonatal combined immune-prophylaxis. Unfortunately, in women presenting high levels of viremia (serum HBV DNA >10^6 copies/mL), neonatal immune-prophylaxis can have unacceptably high rates of failure (9%) [10].

Based primarily on in vivo preclinical data, FDA currently rates telbivudine and tenofovir as pregnancy category B ("Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women"), and lamivudine as pregnancy category C ("Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). However, in HIV-infected pregnant women, the use of tenofovir and lamivudine to prevent HIV transmission has not been linked to any significant safety concerns for either the mother or the newborn.

In conclusion, in pregnant women with chronic HBV infection, the administration of lamivudine, telbivudine, and tenofovir reduces the rate of MTCT and, although limited, safety data of clinical practice suggest no increased risk of adverse maternal or fetal outcomes. Larger-scale randomized controlled trials using tenofovir are ongoing, and their results are eagerly awaited. In the meantime, the treatment of HBeAg positive women with high HBV DNA level (>10^6 copies/mL; 200,000 IU/mL) with antiviral agents in the third trimester is recommended to prevent MTCT.

53.2.1.4 HBV in Children

In children and adolescents, all the currently approved therapeutic agents for chronic HBV show acceptable safety profiles and oral antivirals are safe and well tolerated. The side effects of IFN are similar to that reported for adults,

Table 53.1 Nucleo(s)tide analogues for HBV treatment

	Dosage	Pharmacokinetic tips	Route of drug elimination	Adverse reactions	Drug-drug interactions
High barrier to resistance					
Entecavir	• 0.5 mg once daily for naïve patients • 1 mg once daily for patients with lamivudine or telbivudine resistance or with decompensated cirrhosis	• Terminal $t_{1/2}$ 128–149 h • Slightly bound to serum proteins (13%)	Renally excreted	• Headache, fatigue, dizziness, and nausea	
Tenofovir	• 300 mg once daily	• $t_{1/2}$ of 17 h			• Drugs that inhibit or induce OAT1, MRP, Pgp and BCRP Transporters may affect tenofovir exposure • Sofosbuvir, ledipasvir, and velpatasvir increase tenofovir exposures
Tenofovir Alafenamide (TDF)	• 25 mg once daily			• Fewer adverse effects on BMD and kidney function (CLCr, eGFR, proteinuria) than tenofovir	
Low barrier to resistance					
Lamivudine	• 100 mg once daily				
Adefovir dipivoxil	• 10 mg once daily	• $t_{1/2}$ of 5–7.5 h	Renally excreted	• Dose-related nephrotoxicity and tubular dysfunction, manifested by azotemia and hypophosphatemia, acidosis, glycosuria, and proteinuria • Headache, abdominal discomfort, diarrhea, and asthenia	
Telbivudine	• 600 mg once daily	• $t_{1/2}$ of 40–49 h	Renally excreted	• Increased creatine kinase, nausea, diarrhea, fatigue, myalgia, and myopathy	

although transient effects on body weight and growth have been observed. In children, the development of viral resistance to lamivudine and adefovir is observed at least as often as in adults, whereas is less common with entecavir [11].

The decision of starting the pharmacological treatment in children depends on the patient's characteristics (persistently abnormal ALT levels, active disease on liver biopsy) and on the probability of obtaining appropriate therapeutic goals. In some cases, the treatment can improve chronic HBV infection, at least as far as HBV DNA suppression and HBeAg seroconversion are concerned, although the efficacy in preventing chronic liver diseases, e.g. cirrhosis and HCC in young adult life, remains to be demonstrated.

Generally, children in the immune-tolerant phase (ALT levels less than 1.5–2 times the normal upper limit and HBeAg-positivity with high HBV DNA levels) are not typical candidates for pharmacological treatment, because HBeAg seroconversion cannot be obtained. Children with ALT values 10 times over the upper normal range may undergo spontaneous HBeAg seroconversion, and the pharmacological treatment can be started only after several months of observation.

New therapeutic options for chronic HBV infection in childhood will be available in the next future, since entecavir has recently been shown to be safe and effective in children, and data regarding the safety of pegylated IFN and tenofovir are expected soon. Children in the immune-tolerant phase have not experienced substantial benefit from prolonged treatment with nucleos(t)ide analogues, moreover the risk of developing antiviral drug resistance to the drug used and structurally-related analogues should be considered. The only exception could be represented by those immune-tolerant children undergoing immunosuppressive therapy and chemotherapy, or receiving stem cell or solid organ transplantation [11]. In conclusion, the selection and timing of patient treatment is very critical in childhood and adolescence.

53.3 Hepatitis C Virus (HCV) Infection

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease [12], with a very variable long-term course, ranging from minimal histological changes to extensive fibrosis, cirrhosis and HCC.

The number of chronically infected individuals is about 71 million worldwide [12, 13], but it should be noticed that many patients are unaware of their infection.

Clinical care for patients with HCV-related liver disease has advanced dramatically in recent years as a result of a better understanding of HCV pathophysiology, and the consequent improvement of prevention, diagnosis, and especially pharmacological therapy.

The principal end-point of HCV therapy is to cure the infection with a very low chance of relapse, thus obtaining a sustained virological response (SVR). SVR can be defined an undetectable HCV RNA after 12 weeks (SVR12) or 24 weeks (SVR24) of treatment completion. In patients without cirrhosis, this goal is generally associated with improvement or disappearance of liver necroinflammation and fibrosis and normalization of liver enzymes, whereas in patients with advanced fibrosis or cirrhosis, the risk of life-threatening complications still exists. Moreover, SVR is associated to reversal of a number of extra-hepatic manifestations related to HCV infection and to a significant reduction of all-cause mortality [14].

53.3.1 Treatment Strategies for HCV

HCV has been treated for many years with a prolonged regimen of IFN-α (or PegIFN-α) with or without ribavirin. Nevertheless, both efficacy and tolerability of these therapeutic regimens were not satisfactory. Recently, several orally administered antivirals, directly targeting HCV life cycle (the so-called direct antiviral agents-DAAs) have been approved for HCV treatment, and can be used alone or in combination to enhance their efficacy. They are characterized by a favorable toxicological profile, and can be taken for a limited period of time to achieve SVR rates of at least 90% in most patients. In some cases, ribavirin is still used with DAAs to improve their therapeutic efficacy.

Three are the major targets of available DAAs:

- The non-structural (NS) protein 3 protease, molecular target of paritaprevir, grazoprevir, voxilaprevir and glecaprevir
- The NS5B polymerase, molecular target of sofosbuvir and dasabuvir
- NS5A, molecular target of ledipasvir, velpatasvir, ombitasvir, elbasvir and pibrentasvir.

53.3.1.1 Ribavirin

Ribavirin is a purine nucleoside analogue that inhibits viral replication. The mechanism(s) of action are still unknown in vivo, but several immunomodulatory and antiviral effects have been observed *in vitro* (e.g. inhibition of HCV RNA-dependent RNA polymerase, depletion of GTP through inhibition of inosine 5′-monophosphate dehydrogenase, increase in viral mutagenesis, conversion of the T-helper cell from phenotype 2 to 1, induction of IFN-stimulated genes, and modulation of natural killer cells). Currently, ribavirin is not administered in monotherapy, but in combination with other direct-acting antivirals (DAAs) for treating chronic HCV infection only in specific clinical conditions. The possible associations between ribavirin and DAAs are described in details below.

53.3.1.2 Direct-Acting Antivirals (DAAs)

This paragraph discusses the DAAs which are available in Europe in 2018 [14]. Their posology, pharmacokinetic profiles and possible drug-drug interactions are listed in Table 53.2.

Sofosbuvir

Sofosbuvir, a nucleotide analog potently inhibiting NS5B polymerase in HCV, has shown high efficacy in combination with several other drugs against HCV. Generally, a sofosbuvir-based regimen ranging from 12 to 24 weeks is well tolerated. In urine, the major sofosbuvir metabolite is GS-331007, its dephosphorylated nucleoside (78%), while 3.5% is recovered as unmodified drug. Sofosbuvir is transported by P-gp, whereas cytochrome P450 is not involved in its metabolism. Since no potential drug-drug interactions with other antiviral agents are reported, sofosbuvir can be used in association with such drugs.

The main concern for drug-drug interactions is related to amiodarone. Patients taking this drug should not be treated with sofosbuvir-based regimens since the risk of life-threatening arrhythmias may not be excluded. The risk of cardiac toxicity of sofosbuvir when used in monotherapy is still controversial.

Combination Regimens

Sofosbuvir and Ledipasvir

Patients with mild-to-moderate renal impairment do not require dose adjustment of this combination regimen, whereas in case of severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease, no dose adjustment has yet been proposed. Co-administration with P-gp substrates (e.g. digoxin and dabigatran) and drugs transported by both P-gp and BCRP proteins (e.g. aliskiren, amlodipine, buprenorphine, carvedilol, cyclosporine) require patient strict monitoring. As for sofosbuvir, the coadministration

Table 53.2 DAAs for HCV treatment

	Dosage	Pharmacokinetic tips	Route of drug elimination	Adverse reactions	Drug-drug interactions
Pangenotypic drugs and combinations					
Sofosbuvir	Tablets containing 400 mg of sofosbuvir—one tablet once daily	Time-independent, near-linear pharmacokinetics across a range of doses	80% renally excreted as metabolite GS-331007, 15% eliminated in feces	• Fatigue and headache • Slight elevations of creatine kinase, amylase and lipase in combination with ribavirin	• Inducers of P-gp (rifampicin, carbamazepine, phenytoin or St. John's wort) significantly decrease plasma concentrations with rifabutin, rifapentine and modafinil • Amiodarone (risk of life-threatening arrhythmias)
Sofosbuvir/ velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir—one tablet once daily	Terminal $t_{1/2}$ of velpatasvir approximately 15 h Velpatasvir: 99.5% protein bound	Biliary excretion of velpatasvir parent drug	• Headache, fatigue and nausea	• P-gp or CYP inducers decrease in sofosbuvir and/ or velpatasvir exposure • Antacids, H2-receptor antagonists and proton pump inhibitors • Efavirenz, etravirine and nevirapine
Sofosbuvir/ velpatasvir/ voxilaprevir	Tablets containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir—one tablet once daily		Biliary excretion of voxilaprevir parent drug	• Headache, diarrhoea and nausea • Risk of gastrointestinal side effects greater than with the combination sofosbuvir/velpatasvir	• Substrates of P-gp, BCRP, OATP1B1 and OATP1B3 transporters may increase the exposure of the co-medications • Rosuvastatin • Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine and topotecan • OATP1B inhibitors • OATP1B substrates • Dabigatran • Pgp and/or CYP inducers • Ethinylestradiol-containing contraception
Glecaprevir/ pibrentasvir	Tablets containing 100 mg of glecaprevir—three tablets once daily and 40 mg of pibrentasvir	$t_{1/2}$ approximately 6 and 23 h, respectively	Biliary excretion	• Fatigue and headache	• Co-administration with glecaprevir/pibrentasvir may increase the concentration of comedications that are substrates of P-gp, BCRP and OATP1B1/3 • Strong P-gp and CYP3A inducers • Pgp, BCRP and OATP1B1/3 inhibitors • Ethinylestradiol-containing contraception
Genotype-specific drugs and combination					
Sofosbuvir/ ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir—one tablet once daily	$t_{1/2}$ of ledipasvir 47 h		• Fatigue and headache	• P-gp inducers decrease both sofosbuvir and ledipasvir plasma concentrations • Amiodarone (risk of fatal bradycardia or asystole) • Rosuvastatin (potential inhibition of hepatic OATP by ledipasvir) • Statins • Antacids, H2-receptor antagonists, proton pump inhibitors decrease concentrations of ledipasvir

Paritaprevir/ ombitasvir/ ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir—two tablets once daily	Protein binding is high (about 99%) for all drugs	Ombitasvir and paritaprevir are eliminated in feces	• Fatigue and nausea	• CYP3A4 substrates • Alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot derivatives, lovastatin, simvastatin, atorvastatin, orally-administered midazolam, triazolam, quetiapine, quinidine, salmeterol, sildenafil • Enzyme inducers
Dasabuvir	Tablets containing 250 mg of dasabuvir—one tablet twice daily (morning and evening)		Excreted in the bile and eliminated in the feces	• Fatigue and nausea	
Grazoprevir/ elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir—one tablet once daily	Extensively binding to plasma proteins Terminal $t_{1/2}$ approximately 31 and 24 h, respectively	Biliary and faecal with <1% recovered in urine	• Fatigue and headache	• CYP3A and Pgp inducers • Strong CYP3A inhibitors • OATP1B1 inhibitors

with amiodarone is contraindicated because of a serious risk of fatal bradycardia or asystole.

The combination sofosbuvir/ledipasvir can be used with all antiretrovirals. However, in tenofovir-containing regimens, tenofovir concentration can rise and renal function should be carefully monitored, if other therapeutic options are not possible. Even efavirenz-containing regimens require caution as tenofovir levels can increased. This concern has been recently solved with the approval of tenofovir alafenamide (TAF), that considerably reduces the risk of this pharmacokinetic interaction.

Sofosbuvir and Velpatasvir

In vitro, three CYP isoforms (CYP2B6, CYP2C8 and CYP3A4) have been found to be responsible for velpatasvir metabolism, whereas *in vivo* velpatasvir is essentially unmodified. Velpatasvir transport is operated by P-gp and BCRP and, to a limited extent, by organic anion transporting polypeptide (OATP) 1B1.

As for ledipasvir, co-medication of velpatasvir and drugs transported by P-gp and/or BCRP need caution, because of the possible increase of their plasma concentration. Therefore, co-administration with P-gp, BCRP, OATP and CYP substrates having a narrow therapeutic window could potentially have clinical consequences due to increased drug exposure.

In HIV-HCV coinfected patients, sofosbuvir/velpatasvir should not be administered with efavirenz, etravirine and nevirapine due to pharmacokinetic interactions and increased risk of toxicity.

Sofosbuvir, Velpatasvir and Voxilaprevir

Since voxilaprevir AUC and maximum concentration were found to be 112–435%, and 147–680% higher, respectively, in the presence of food, the tablet containing these molecules should be taken during meal [14].

Both velpatasvir and voxilaprevir inhibit P-gp, BCRP, OATP1B1 and OATP1B3. In patients with moderate liver cirrhosis (Child-Pugh B patients) the administration of sofosbuvir/velpatasvir/voxilaprevir is not recommended, and is absolutely contraindicated when liver dysfunction becomes severe (Child-Pugh C patients), due to the significant increase of voxilaprevir AUC in these patients.

Proton pump inhibitors can be given at a dose not exceeding 20 mg omeprazole and, if possible, 4 h after sofosbuvir/velpatasvir/voxilaprevir administration, since velpatasvir solubility decreases as pH increases. In HIV-HCV coinfected patients, the co-administration with efavirenz, etravirine and nevirapine and the protease inhibitor associations atazanavir/ritonavir and lopinavir/ritonavir is not recommended. Efavirenz causes a 50% decrease in velpatasvir exposure, whereas atazanavir causes a fourfold increase in voxilaprevir exposure. Tenofovir-based regimens should be monitored for renal adverse events.

Ritonavir-Boosted Paritaprevir, Ombitasvir and Dasabuvir

Paritaprevir is a HCV protease inhibitor predominantly metabolized by CYP3A4 and primarily excreted into the feces.

Ombitasvir is an nonstructural protein 5A (NS5A) inhibitor that predominantly undergoes hydrolysis and is eliminated with the feces. It can be partially subjected to CYP3A4-mediated metabolism.

Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase, undergoing hepatic CYP2C8- and to a lesser extent CYP3A4-mediated metabolism. Its main metabolite is excreted into the bile and eliminated with the feces. In genotype 1 patients, dasabuvir is given in combination with ritonavir/paritaprevir/ombitasvir. Patients with mild liver cirrhosis (Child-Pugh A) don't require dose adjustment, whereas the combination of ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir should not be administered in case of decompensated liver cirrhosis (Child-Pugh B and C).

The antiretroviral drug **ritonavir** is a strong inhibitor of CYP3A4 and markedly increases the plasma concentrations of many drugs metabolized by this cytochrome. Because of this characteristic, it is used as a pharmacokinetic enhancer of paritaprevir, but, if co-administered with other CYP3A4 substrates, can lead to serious adverse events. For this reason a wide range of drugs are contraindicated in association with ritonavir (i.e. alfuzosin, amiodarone, astemizole, terfenadine). Since the administration of enzyme inducers (carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, enzalutamide) may compromise antiviral efficacy, and enzyme inhibitors (azole antifungals, some macrolide antibiotics) may increase paritaprevir exposure, the co-administration of a ritonavir-boosted regimen with these drugs is not recommended.

Paritaprevir, dasabuvir and ritonavir may inhibit drug transporters. In particular, the drug inhibits OATP1B1/B3, P-gp and BCRP, whereas dasabuvir and ritonavir inhibit P-gp and BCRP, but not OATP. Because of the metabolic profile of these drugs and ritonavir characteristics, drug-drug interactions during these regimens cannot be excluded. Therefore, based on the guidelines of both the European Medicines Agency and the US Food and Drug Administration, a comprehensive program investigating the drug-drug interactions occurring with these drugs has been started. Thus, drug interactions need to be carefully considered and the therapeutic regimen could require dosage adjustment, modifications of the timing of administration or additional monitoring. Additional caution has to be taken in HIV co-infected patients, in which ritonavir should be avoided if they are treated with atazanavir and darunavir. Other drugs used against HIV, such as efavirenz, etravirine, cobicistat and nevirapine are not indicated, whereas rilpivirine should only be used under ECG monitoring, because of the risk of cardiac toxicity.

Grazoprevir and Elbasvir

According to in vitro data, grazoprevir and elbasvir are partially metabolized by CYP3A4, although no metabolites have been detected in plasma [14]. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate of P-gp. In patients with moderate or severe hepatic impairment (Child-Pugh B and C) the administration of this combination is not recommended due to pharmacokinetic concerns, whereas renal impairment is not a contraindication and doesn't require any dose adjustment. Drugs metabolized by CYP3A and transported by Pgp need additional monitoring and often dose reduction. Currently, only nucleos(t)ide reverse transcriptase inhibitors can be used as antiretrovirals in combination with grazoprevir and elbasvir (e.g. abacavir, lamivudine, tenofovir).

Glecaprevir and Pibrentasvir

The combination of glecaprevir and pibrentasvir is contraindicated in case of moderate or severe hepatic impairment (Child-Pugh B or C). As with the grazoprevir/elbasvir combination, co-administered drugs whose disposition depends on CYP3A require additional caution or dose reduction. Doses of omeprazole greater than 40 mg may lead to a profound decrease in glecaprevir concentrations, since glecaprevir solubility decreases as pH increases, even though the co-administration has not yet been rigorously studied. Glecaprevir/pibrentasvir is contraindicated with atazanavir-containing regimens in HIV coinfected patients and is not recommended with other HIV protease inhibitors and with inducing non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine and nevirapine). The other antiretroviral drugs, including cobicistat, can be co-administered in elvitegravir-containing regimens.

In conclusion, because of their efficacy, safety and tolerability, the best options for all both "treatment-naïve" and "treatment-experienced" patients, including those without cirrhosis and those with either compensated (Child-Pugh A) and decompensated (Child-Pugh B and C) cirrhosis, are represented by DAA-based regimens without interferon (IFN) and ribavirin. The therapeutic choice has to be based on the HCV genotype/subtype, the severity of liver disease, and/or prior therapy. In HIV-coinfected patients, treatment or dose adjustments may be required due to drug-drug interactions.

As mentioned before, HCV has six main genotypes (labelled 1–6) with multiple subtypes. The most frequent genotypes worldwide are 1–3. As described in details below, genotyping is fundamental for planning the HCV treatment and personalize HCV therapy. The recommended therapeutic regimens illustrated below are listed in the EASL [14] and American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) [15] guidelines. AASLD-IDSA also suggest possible alternative regimens (www.hcvguidelines.org).

- **Genotype 1**
  - **Genotype 1a**
    For treatment-naive patients with HCV genotype 1a, characterized by a higher relapse rate than patients with HCV genotype 1b, there are four regimens of similar efficacy, i.e. sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir, grazoprevir/elbasvir.
  - **Genotype 1b**
    For treatment-naive patients infected with HCV genotype 1b, five recommended regimens are available: sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir, grazoprevir/elbasvir and paritaprevir/ombitasvir/dasabuvir boosted with ritonavir.

    Patients with genotype 1 HCV infections who cannot be subtyped should be treated as genotype 1a patients, since this subtype has a greater risk of relapse when compared with genotype 1b.
- **Genotype 2**
  Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are the two first line treatment regimens recommended for genotype 2 patients, both treatment-naïve and experienced.
- **Genotype 3**
  The response of genotype 3 to DAAs currently available is less satisfying hat of genotypes 1 and 2. According to AASLD guidelines, the recommended regimens are sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, whereas EASL guidelines also indicate sofosbuvir/velpatasvir/voxilaprevir as a further option.
- **Genotype 4**
  According to the EASL guidelines, patients with HCV genotype 4 have four therapeutic options: glecaprevir/pibrentasvir, grazoprevir/elbasvir and two sofosbuvir-based regimens, namely ledipasvir/sofosbuvir and sofosbuvir/velpatasvir.
- **Genotype 5 or 6**
  Although few data are available for patients infected with HCV genotype 5 or 6, based on emerging data, sofosbuvir/ledipasvir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir are currently recommended [16].

53.4 Future Perspectives for Hepatitis Treatment

53.4.1 Future Treatment Options for HBV

The main goal of HBV infection treatment is the clearance of HBsAg, with the aim of avoiding the risk of post-treatment virologic relapse and liver disease progression, and decreasing HCC risk. Since HBV DNA is integrated into the host genome, its eradication may not be feasible,

but treatment of earlier stages of liver disease would theoretically have a greater impact on reducing the risk of developing HCC. Currently, pre-clinical and early clinical studies are investigating two novel treatment options, i.e. direct antivirals and immunotherapeutic agents. The formers, which have been designed to decrease HBsAg release in serum, include HBV entry inhibitors, drugs silencing or disrupting covalently closed circular DNA (cccDNA), genetic approaches by means of siRNA or anti-sense oligonucleotides targeting viral transcripts, and modulators of nucleocapsid assembly. As immunotherapeutic agents, toll-like receptors 7 (TLR7) agonists and other agents that are able to restore INF responsiveness or affect other antiviral innate pathways are currently under investigation. Moreover, the ability of some new cancer immunotherapies to restore anti-tumor adaptive immunity in chronic HBV patients has been investigated.

In the future, the goal of new antiviral therapies is likely to be represented by a combination therapy, targeting multiple pathways of HBV and restoring immune response against HBV.

As far as the HBV-HDV coinfection is concerned, this is treated with PegIFN-α, nevertheless the success rate is low. Several clinical trials are evaluating new candidates to be used mainly in combination with PegIFN-α and/or NAs. Some of these compounds are HBV/HDV entry inhibitors (Myrcludex-B) [17, 18], nucleic acid polymers that inhibit the release of HBsAg [19] and inhibitors of the prenylation of the large HDV antigen [20]. In order to rescue patients who do not respond to PegIFN-α or to improve the success rate of treatment of naïve patients, the enrolment in these new clinical trials should be considered as a possible choice option.

53.4.2 Future Perspectives for the Treatment of HCV

At present, several studies are investigating new agents for the treatment of HCV, although in recent years several drugs with high successful rate have gained approval. Some issues still remain to be addressed and represent a challenge for future drug development. For example, the successful rates of available agents is very high in most populations that have access to a cure, but not in all patient sub-populations, including cirrhotic genotype 3 patients, individuals with decompensated cirrhosis, and those who fail DAA treatment. Moreover, new techniques for HCV testing and diagnosis, and increasing access to expensive therapies to the whole world population represent future research goals.

Self Study

Questions

1. Which statement is true?
   (a) Ritonavir is approved for treatment of HCV of all genotypes.
   (b) Only sofosbuvir-based regimens are indicated for genotype 2 HCV.
   (c) The antiretroviral drug **ritonavir** is a strong inhibitor of CYP3A4 and is used in association with DAAs as a pharmacokinetic enhancer of paritaprevir.
   (d) Sofosbuvir is transported by P-gp, and metabolized by cytochrome P450 3A4.
2. Which statement is true?
   (a) Interferon is usually administered for the entire life of the patient.
   (b) Nucleos(t)ide analogues (NAs) have all high barrier to HBV resistance.
   (c) Mother-to-child transmission is never occurring for HBV.
   (d) Entecavir and tenofovir are classified as drugs with high barrier to HBV resistance.

Answers

1. Which statement is true?
   (a) Ritonavir is part of a combination therapy indicated for genotype 1b HCV therapy.
   (b) Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are the two first line treatment regimens recommended for genotype 2 patients.
   (c) **The antiretroviral drug ritonavir is a strong inhibitor of CYP3A4 and markedly increases the plasma concentrations of many drugs metabolized by this cytochrome. Because of this characteristic, it is used as a pharmacokinetic enhancer.**
   (d) Sofosbuvir is transported by P-gp, whereas cytochrome P450 is not involved in its metabolism.
2. Which statement is true?
   (a) Interferon therapy has generally a limited duration.
   (b) Among the five NAs approved for chronic HBV treatment (lamivudine, adefovir, entecavir, telbivudine and tenofovir), three (lamivudine, adefovir, telbivudine) have low barrier and two (entecavir, tenofovir) high barrier to HBV resistance.
   (c) The perinatal or mother-to-child transmission (MTCT) of HBV is one of the major risk factors of chronic HBV infection.

(d) **Differently from the other NAs, entecavir and tenofovir have a high barrier to HBV resistance.**

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