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Review

Current antiviral drugs and their analysis in biological materials – Part II: Antivirals against hepatitis and HIV viruses

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ABSTRACT

This review is a Part II of the series aiming to provide comprehensive overview of currently used antiviral drugs and to show modern approaches to their analysis. While in the Part I antivirals against herpes viruses and antivirals against respiratory viruses were addressed, this part concerns antivirals against hepatitis viruses (B and C) and human immunodeficiency virus (HIV).

Many novel antivirals against hepatitis C virus (HCV) and HIV have been introduced into the clinical practice over the last decade. The recent broadening portfolio of these groups of antivirals is reflected in increasing number of developed analytical methods required to meet the needs of clinical terrain. Part II summarizes the mechanisms of action of antivirals against hepatitis B virus (HBV), HCV, and HIV, their use in clinical practice, and analytical methods for individual classes. It also provides expert opinion on state of art in the field of bioanalysis of these drugs. Analytical methods reflect novelty of these chemical structures and use by far the most current approaches, such as simple and high-throughput sample preparation and fast separation, often by means of UHPLC–MS/MS. Proper method validation based on requirements of bioanalytical guidelines is an inherent part of the developed methods.

Contents

1. Introduction

This review is a continuation of Part 1 entitled "Current antiviral drugs and their analysis in biological materials – Part I: Antivirals against respiratory and herpes viruses" [1]. This part deals particularly with antivirals against hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Most of these drugs are on the list of World Health Organization (WHO) essential medicines of March (2017) documenting their irreplaceable role in managing HBV, HCV, and HIV infections. History of HIV antivirals (antiretrovirals) started in mid 1980s with nucleoside reverse transcriptase inhibitor (NRTI) zidovudine subsequently progressing to other molecules from this class, and then to

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other groups with different mechanisms of action such as protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and finally to integrase strand transfer inhibitors (INSTIs) as well as entry inhibitors [2]. Applying patient-tailored antiretroviral regimens we are capable to reduce HIV blood concentrations to undetectable values within weeks and induce immunity via CD4 T-cell gain. However, up to date, we are still not able to fully cure the disease [3].

On the other hand, development of HBV and mainly HCV antivirals has experienced rapid progress relatively recently. HBV infection can be suppressed by NRTI lamivudine and acyclic nucleoside phosphonate analogue adefovir dipivoxil. Nevertheless, drugs such as prodrugs of tenofovir, which is structurally similar to adefovir, and nucleoside analogue entecavir, both revealing higher effectivity and high genetic barrier to drug resistance, are currently preferred [4–6]. Knowledge on HCV life cycle and processes required for HCV proliferation has led to development of direct-acting antiviral agents (DAAs) representing major advance in HCV infection treatment. DAAs include NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors and in combination regimens they can cure up to 90% of patients [7]. This part of the review outlines mechanisms of actions and clinical use of antivirals against HBV, HCV, HIV, summarizes available bioanalytical methods, and provides expert opinion on experimental approaches suitable for determination of these antivirals in matrices as distinct as experimental buffer to complex human tissue.

2. Antivirals against hepatitis viruses

2.1. Mechanism of action and use in practice

Pharmacotherapy is available for HBV and HCV infections caused by the hepatitis viruses. Both viruses are blood-borne and may be transmitted by sexual contact, vertical transmission from mother to developing fetus, and parenterally by needle sharing and blood transfusion. HBV and HCV families are not genetically uniform [8,9]. HBV strains are divided into eight genotypes belonging to more than 24 subtypes while HCV strains are classified into seven major genotypes with genotypes 1 and 2 being responsible for most of infections worldwide [10]. Symptoms of HBV and HCV infection include fatigue, jaundice, anorexia, abdominal pain, dark urine, nausea, vomiting, and/or joint pain. Unlikely to HBV infection, signs of HCV infection encompass bleeding easily, ascites, hepatic encephalopathy, and spider angiomas. Chronic HBV and more frequently HCV infection lead to cirrhosis, portal hypertension, liver failure, and liver cancer [11–13]. According to WHO global health survey, HBV or HCV infections currently cause more than 1.25 million deaths per year. Importantly, in days when HIV infection was transformed to manageable chronic disease, co-infection with HCV remains the most common cause of death in these patients [14].

Carbocyclic nucleoside entecavir, thymidine analogue telbivudine, and/or acyclic nucleoside phosphonate analogue adefovir given as oral prodrug adefovir dipivoxil are exclusively used in HBV treatment while nucleoside inhibitors of reverse transcriptase (NRTIs) lamivudine and two orally used prodrugs of tenofovir, tenofovir disoproxil fumarate, and tenofovir alafenamide, structurally belonging to acyclic nucleoside phosphonate analogues, are approved for treatment of HBV and HIV, as well as for their coinfection. Anti-HBV drugs must be converted by kinases to triphosphate (entecavir, telbivudine, and lamivudine) or diphosphate form (tenofovir and adefovir) and the active forms compete with natural substrates leading to chain termination and/or inhibition of HBV DNA polymerase [15]. Mechanism of entecavir action is more complex as it inhibits three specific functions of HBV DNA polymerase: (i) priming of the HBV DNA polymerase, (ii) reverse transcription of the negative strand from the pre-genomic mRNA, and (iii) synthesis of positive strand HBV DNA [16]. Therefore, entecavir is the most potent agent for the treatment of patients with chronic HBV infection including those resistant to lamivudine [17,18]. Resulting from effectivity, good tolerability and a high genetic barrier to drug resistance, this compound is suitable as the first-line therapy for children aged two and older [19].

Table 1
Currently used antivirals against HBV and HCV (April 2017).

Drug group	Generic name of a compound	Abbreviation	Infectious agent	Mechanism(s) of action
NRTIs	Lamivudine	3TC	HBV, HIV	Nucleoside analogue, triphosphate form inhibits viral polymerase and by competing with dCTP inhibits DNA synthesis
	Tenofovir disoproxil fumarate	TDF	HBV, HIV	Acyclic nucleoside phosphonate analogues, prodrugs of tenofovir; tenofovir diphosphate inhibits HIV reverse transcriptase and HBV DNA polymerase by competing with dATP
	Tenofovir alafenamide	TAF	HBV, HIV	
Acyclic nucleoside phosphonate analogues	Adefovir dipivoxil	ADV	HBV	Prodrug of adefovir; adefovir diphosphate inhibits HBV DNA polymerase by competing with dATP
Nucleoside analogues	Entecavir	ETV	HBV	Inhibits three specific priming of the HBV DNA polymerase, reverse transcription of the negative strand from the pre-genomic mRNA, and synthesis of positive strand HBV DNA
	Telbivudine	LdT	HBV	Inhibits the activity of HBV viral polymerase
NS3/4A protease inhibitors	Simeprevir	SMV	HCV	Block maturation of virions by inhibition of proteolytic enzyme NS3A4
	Asunaprevir	ASV	HCV	
	Vaniprevir	VPV	HCV	
	Paritaprevir	PTV	HCV	
	Grazoprevir	GZR	HCV	
NS5A protein inhibitors	Ledipasvir	LDV	HCV	NS5A inhibition likely leads to dysregulation of the structural stability, dimerization, or subcellular distribution of NS5A; causes block of HCV RNA replication
	Daclatasvir	DCV	HCV	
	Ombitasvir	OBV	HCV	
	Velpatasvir	VEL	HCV	
	Elbasvir	EBR	HCV	
NS5B polymerase inhibitors	Dasabuvir	DAS	HCV	Inhibits HCV NS5B RNA polymerase
	Sofosbuvir	SOF	HCV	
Nucleoside analogs	Ribavirin	RBV	HCV, RSV	Ribavirin triphosphate inhibits viral RNA synthesis

NRTIs = nucleoside/nucleotide inhibitors of reverse transcriptase.