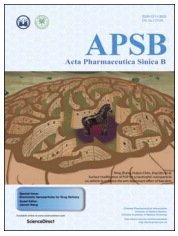
Acta Pharmaceutica Sinica B ▮▮▮▮;▮(▮):▮▮▮–▮▮▮

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Anti-retroviral drugs: Current state and development in the next decade

Xingquan Zhang

Division of Infectious Diseases, Department of Medicine, School of Medicine, University of California, San Diego, CA 92093, USA

Received 2 December 2017; received in revised 12 January 2018; accepted 21 January 2018

KEY WORDS

Antiretroviral drugs;
Long-acting formulations;
Attachment inhibitors;
Maturation inhibitors;
Nanomedicine

Abstract The pace of discovery of new antiretroviral (ARV) drugs has slowed, although the efficacy and safety of once-daily fixed dose combinations have been extensively investigated. Several traditional ARV drugs remain in phase III clinical trials. This review summarizes current information on ARV drugs in phase III clinical trials and focuses on the development of ARV drugs in the next decade.

E-mail address: xiz002@ucsd.edu (X. Zhang).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

https://doi.org/10.1016/j.apsb.2018.01.012

Please cite this article as: Zhang Xingquan. Anti-retroviral drugs: Current state and development in the next decade. *Acta Pharmaceutica Sinica B* (2018), https://doi.org/10.1016/j.apsb.2018.01.012

1. Introduction

By the end of 2017, United States Food and Administration (US FDA) had approved 43 anti-retroviral drugs for clinical use which include 29 single-tablets and 14 fixed-dose combinations (FDCs). The intensity of the search for novel antiretroviral (ARV) compounds has slowed over the last 10 years and several traditional agents are still in phase III clinical trials. In the next decade, to improve drug safety, adherence and efficacy, the development of new anti-HIV-1 drugs will focus on long-acting formulations, oral attachment inhibitors, maturation inhibitors and new initiatives to cure the disease.

In the first decade of ARV drug therapy, these agents did not fundamentally change the destiny of those with HIV infection, although they could decrease virus load, increase $CD4^+$ cell number and prolong survival over the short term. The major shortcomings were drug toxicity, drug resistance and high drug cost. Combination-based ARV therapy (ART) was introduced in 1996, which led to effectively sustained HIV suppression, significantly recovered immune function, markedly improved clinical symptoms and notably extended lifespan. In the third decade, with further development of ARV drugs and the availability of multiple ART regimens and FDCs, acquired immune deficiency syndrome (AIDS) has become a chronic, manageable and infectious disease. It is noted that in the last several years, instead of the discovery of new ARV drugs, development of effective and well-tolerated once-daily FDCs has been extensively investigated, but several traditional ARV drugs remain in phase III clinical trials. This review introduces current ARV drugs in phase III clinical trials and summarizes the development of ARV drugs over the next decade. All of the 43 FDA-approved drugs are listed here, but additional specialized reviews will be required to address new trends towards the cure of this disease.

2. Anti-retroviral drugs approved by FDA

The first AIDS cases were reported in 1981 in United States[1,2]. The human immunodeficiency virus (HIV) was defined as etiologic microorganism in 1983[3,4]. Just four years later, the first HIV medicine Zidovudine was approved by US FDA and quickly opened the new era for anti-retroviral chemotherapy. In the following thirty years, the FDA approved a total of 43 anti-retroviral drugs including 29 single-tablets and 14 FDCs therapeutics. These agents are classified into eight categories of ARV drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), entry inhibitors (EIs), pharmacokinetic enhancers (PEs) and fixed-dose combinations (FDCs, Table 1[5–7]).

3. Classical ARV drugs in phase III clinical trials

3.1. Tenofovir alafenamide (TAF)

TAF is a nucleotide transcriptase inhibitor (Fig. 1)[5,8]. Tenofovirs disoproxil (TDF), a new prodrug of tenofovir, has a similar structure and is in clinical use. Initially TAF was designed to improve TDF-induced renal and bone toxicity. TAF has achieved 50% effective concentrations (EC_{50}) at 11.0 and 9.7 nmol/L in $CD4^+$ T cells and macrophage, respectively, and decrease of plasma tenofovir by 90%. As compared with TDF, TAF demonstrated several important improvements. The drug can be formulated into small tablets of FDCs, has a low manufacturing cost, and shows highly reduced kidney and bone toxicity. Therefore, TAF is becoming a preferred substitute for TDF with better efficacy. Several clinical studies of TAF combinations, including elvitegrave/cobicistat/emtricitable/TAF (E/C/F/TAF), rilpivirine/emtricitabine/TAF (R/F/TAF) and emtricitabine/TAF (F/TAF) were reported on November 23, 2015, March 1, 2016 and April 25, 2016.

Phase III open-label studies have evaluated the safety of E/C/F/TAF in virologically-suppressed adults with mild-to-moderate renal impairment and in treatment-naïve 12–17 year olds[9]. Whereas E/C/F/TDF is typically reserved for patients with creatinine clearance (CrCl) of at least 70 mL/min, E/C/F/TAF can be used with a pre-treatment estimated CrCl of as low as 30 mL/min[9]. Phase III randomized, double-blind clinical trials evaluating the safety and efficacy of switching to R/F/TAF in HIV-positive individuals who are virologically suppressed by either R/F/TDF or efavirenz/F/TDF (EVF/F/TDF)are under investigation[10]. In other phase III studies, 668 and 330 HIV-1 positive patients were recruited in F/TAF and F/TDF groups separately. Through week 48, the success cases of virological inhibition (HIV-1 RNA <50 copies per mL) were maintained in 314 (94%) of patients in the F/TAF group compared with 307 (93%) in the F/TDF group (a difference of 1.3%, 95% CI –2.5 to 5.1), indicating the non-inferiority of F/TAF to F/TDF. Seven patients in F/TAF (2%) and three (1%) in the F/TDF group discontinued treatment due to adverse events. There were no cases of proximal tubulopathy reported in these studies[11].

3.2. Doravirine

Doravirine is a highly specific non-nucleoside reverse transcriptase inhibitor (Fig. 1)[5,12,13]. The half maximal inhibitory concentrations (IC_{50}) are only 12, 9.7 and 9.7 nmol/L against the wild type HIV (WT) and 103 N and Y181C reverse transcriptase (RT) mutants, respectively. Doravirine exhibited consistent anti-HIV activities against 10 different HIV-1 subtype viruses, that the resistance suggesting that doravirine is superior overall to that *efavirenz* and comparable to that of etravirine (ETR) and RPV. A two-drug *in vitro* combination study reported that doravirine had no antagonistic actions in the antiviral activity of 18 other FDA-licensed anti-HIV drugs. *In vivo*, doravirine demonstrated robust antiviral activity and good tolerability. Data from a 48 week phase II clinical trial showed that virologic suppression (<40 copies/mL) rates were achieved in 84% of inpatients with viral loads $>100{,}000$ copies/ml. In addition, drug-related adverse events, including diarrhea, dizziness, and abnormal dreams, were infrequent in the dorvirine group *vs.* the EFV group (56.5% *versus* 31.5%). Doravirine is currently undergoing its phase III clinical development.

3.3. Bictegravir (BIC, GS-9883)

BIC[5,14] is a novel unboosted HIV-1 integrase strand inhibitor (Fig. 1). It inhibits HIV replication in both T-cells lines and in primary human T lymphocytes, with EC_{50} values ranging from 1.5 to 2.4 nmol/L and selectivity indices of up to 8700. BIC demonstrates synergy of anti-HIV effects *in vitro* when combined with TAF, emtricitabine and darunavir. BIC is showing an

Please cite this article as: Zhang Xingquan. Anti-retroviral drugs: Current state and development in the next decade. *Acta Pharmaceutica Sinica B* (2018), https://doi.org/10.1016/j.apsb.2018.01.012