Post-print of Anti-Hepatitis B Virus Drug Market Analysis

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Abstract

Hepatitis B virus (HBV) is the primary causative agent of viral hepatitis B and remains a global public health challenge. Interferon and nucleos(t)ide analogues constitute the main anti-HBV agents approved and marketed both domestically and internationally. Tenofovir and entecavir hold a substantial share of the anti-HBV drug market abroad, whereas the market share of earlier-introduced lamivudine and adefovir dipivoxil has been declining annually due to concerns regarding tolerability and safety. Thirty-nine novel anti-HBV agents are currently in clinical development abroad. Oral nucleos(t)ide analogue drugs are more frequently utilized in domestic clinical practice, with entecavir alone accounting for nearly half of the anti-HBV drug market in recent years. The top 10 enterprises in urban retail of anti-HBV drugs command 91.8% of the total retail market share, indicating high market concentration. Although a significant gap persists between domestic R&D capabilities for novel hepatitis B drugs and those in Europe and the United States, over 20 enterprises engaged in R&D, including Dongyangguang and Chia Tai Tianqing, have emerged under the impetus of domestic innovation policies and have achieved certain accomplishments. In response to the development challenges of anti-HBV drugs in China, this study proposes policy recommendations including continued improvement of medical insurance policies for anti-HBV drugs, deployment and implementation of major R&D projects such as special programs for hepatitis B, and promotion of deep integration among industry, academia, research, and application.

Full Text

Preamble

Analysis of the Anti-Hepatitis B Virus Drug Market

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Abstract

Hepatitis B virus (HBV) is the primary pathogen causing viral hepatitis B and remains a global health challenge. Interferon and nucleos(t)ide analogs constitute the main classes of anti-HBV drugs approved for market entry both domestically and internationally. Tenofovir and entecavir dominate the international anti-HBV drug market, while earlier agents such as lamivudine and adefovir dipivoxil have experienced declining market share due to issues with tolerance and safety. Currently, 39 novel anti-HBV drugs are in clinical development worldwide. In China, oral nucleos(t)ide analogs are more commonly used clinically, with entecavir alone accounting for nearly half of the domestic anti-HBV drug market in recent years. The top 10 enterprises in urban retail sales of anti-HBV drugs command 91.8% of the total retail market, indicating high market concentration. Although China' s R&D capabilities for novel anti-HBV drugs still lag significantly behind Europe and the United States, over 20 domestic companies, including HEC Pharma and Chia Tai Tianqing, have engaged in drug development under national innovation policies and have achieved certain accomplishments. Based on an analysis of China' s anti-HBV drug development challenges, this paper proposes policy recommendations including further improvement of medical insurance coverage for anti-HBV drugs, implementation of major R&D programs for hepatitis B, and promotion of deep integration between industry, academia, and research institutions.

Keywords: Hepatitis B; Antiviral drugs; Interferon; Nucleos(t)ide analogs

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Hepatitis B virus (HBV) is the primary pathogen causing viral hepatitis B. According to the WHO Global Hepatitis Report 2017, approximately 325 million people worldwide were living with chronic hepatitis B or C infection, with 257 million chronically infected with HBV. Viral hepatitis caused 1.34 million deaths in 2015, and nearly 50% of chronic hepatitis patients are concentrated in developing countries such as China and Brazil. China has an estimated 90 million HBV-infected individuals, representing 25% of the global burden.

HBsAg clearance and HBeAg seroconversion are considered markers of effective hepatitis B treatment. The U.S. Food and Drug Administration (FDA) has approved two main categories of anti-HBV drugs: (1) interferons (IFN), including conventional interferon-α and long-acting pegylated interferon-α, which exert antiviral effects by modulating immune function and producing antiviral proteins; and (2) nucleos(t)ide analogs, including nucleoside analogs such as lamivudine, telbivudine, and entecavir, as well as nucleotide analogs such as adefovir dipivoxil and tenofovir disoproxil fumarate [4,5]. Both interferons and nucleos(t)ide analogs have limitations: interferons can improve patient symptoms but achieve remission in only 20-50% of cases, require intramuscular injection, have high adverse event rates with long-term use, and are unsuitable for

patients with hepatic decompensation. Nucleos(t)ide analogs effectively inhibit viral replication but require long treatment courses, readily induce primary or secondary drug resistance, and frequently cause viral rebound upon discontinuation [6-8]. This paper analyzes the domestic and international anti-HBV drug markets and proposes targeted recommendations to address challenges in China' s anti-HBV drug market and R&D landscape.

1.1 Approval Status

In 1986, Intron A (interferon α-2b) became the first interferon approved by the FDA, receiving approval for chronic hepatitis B treatment in 1992. PegIntron (pegylated interferon α-2b) was the first long-acting interferon approved by both the EU and FDA in 2000-2001, retaining Intron A' s advantages while requiring only weekly injections for improved patient convenience. In 2005, Pegasys (pegylated interferon α-2a) became the only pegylated interferon approved for chronic hepatitis B treatment by the United States, China, and the European Union. Lamivudine (Epivir), developed by GlaxoSmithKline, was the world' s first nucleoside analog for hepatitis B treatment, approved by the FDA in 1998. To date, 19 lamivudine products from different manufacturers have reached the market. Subsequently, adefovir dipivoxil from Gilead Sciences, entecavir from Bristol-Myers Squibb, and telbivudine from Novartis received regulatory approval. Since its 2008 approval, 13 tenofovir products have been marketed. Tenofovir alafenamide fumarate (TAF), a tenofovir prodrug also developed by Gilead, was approved in 2016 .

1.2 Market Situation

As first-line and second-line agents recommended in hepatitis B treatment guidelines, the high-barrier-to-resistance nucleos(t)ide analogs tenofovir and entecavir have maintained annual sales exceeding $1 billion during 2014-2017, commanding a substantial share of the international anti-HBV drug market. In contrast, earlier agents lamivudine and adefovir dipivoxil have experienced 逐年递减的市场份额 due to tolerance and safety concerns, now maintaining only minimal market presence. Interferon products Pegasys and PegIntron retain some market share, but their overall sales have also declined annually; PegIntron' s 2016 sales of 259 million Swiss francs were less than half of its 2015 sales (538 million Swiss francs) .

1.3 R&D Landscape

Since HBV covalently closed circular DNA (cccDNA) persists in hepatocyte nuclei, current antiviral drugs—including nucleos(t)ide analogs and interferons—can only control HBV production rather than eliminate the virus. The primary therapeutic goal is functional cure, defined as sustained HBsAg loss with or without anti-HBs seroconversion and undetectable serum HBV DNA after treatment cessation. Global researchers are actively developing next-generation anti-HBV agents targeting novel pathways. Approaches include direct-acting

antivirals (DAAs) and immunomodulatory therapies. As of July 2018, 39 novel agents were in clinical development.

Direct-acting antivirals target viral replication processes and include TDF prodrugs, siRNAs, entry inhibitors, capsid inhibitors, HBsAg inhibitors, antisense molecules, and RNase H inhibitors, with 21 agents in development. For example, ContraVir is developing TXL (CMX157), a modified tenofovir prodrug that more efficiently enters hepatocytes, acting as an entry inhibitor that establishes innate immune defense pathways. Immunomodulatory approaches target the host immune system to attack HBV and include therapeutic vaccines, innate immune defense pathways, host-targeting agents, and gene editing. Therapeutic vaccines stimulate the immune system for treatment purposes and represent specific active immunotherapy, with protein-based, gene-based, and cell-based formulations. Recombinant HBsAg vaccines are commonly used clinically. GS-4774 is a recombinant, heat-killed, yeast-derived vaccine expressing HBV surface, core, and X antigens [9], demonstrating high safety and tolerability. Gene editing using CRISPR/Cas9 systems for HBV treatment remains preclinical. Additional approaches include monoclonal antibodies, FXR agonists, and T-cell immunotherapy .

2 Domestic Anti-HBV Drug Market

According to China' s National Health Commission Disease Prevention and Control Bureau, viral hepatitis ranked first among Class B infectious diseases nationwide (excluding Hong Kong, Macau, and Taiwan) in 2017, with 1.284 million reported cases—1.002 million (78.06%) being hepatitis B. Viral hepatitis caused 573 deaths, with hepatitis B accounting for 425 (74.17%). These figures underscore China' s enormous hepatitis B market size and drug demand, which will continue to grow rapidly.

In May 2016, WHO adopted the Global Health Sector Strategy on Viral Hepatitis 2016-2021, calling for elimination of viral hepatitis as a public health threat by 2030 (90% reduction in new infections and 65% reduction in mortality). At the 2016 National Health Conference, President Xi Jinping emphasized that "for traditional major infectious diseases such as AIDS, tuberculosis, hepatitis B, and schistosomiasis, we must adopt disease-specific strategies to achieve breakthroughs, consolidate current prevention and control achievements, and continuously reduce epidemic levels." In December 2016, the State Council issued the 13th Five-Year Plan for Health, aiming to reduce HBV infection rates across all populations. In February 2017, the Ministry of Human Resources and Social Security released the National Reimbursement Drug List (2017 Edition), the fourth update since its inception, which newly included tenofovir disoproxil fumarate for hepatitis B treatment. In October 2017, the National Health and Family Planning Commission and 10 other departments jointly issued the China Viral Hepatitis Prevention and Treatment Plan (2017-2020), mandating that regulatory authorities prioritize review and approval pathways for antiviral drugs with significant efficacy and urgent clinical need, while health authorities

gradually include more hepatitis drugs meeting selection criteria in the National Essential Medicines List.

2.2 Enterprise and Approval Status

Domestic anti-HBV drugs comprise two main categories: immunomodulators (interferons) and nucleos(t)ide analogs. Due to greater adverse effects and higher costs associated with interferons (both conventional and pegylated), oral nucleos(t)ide analogs are more widely used clinically.

Between April 2015 and April 2018, the China Food and Drug Administration (CFDA) approved 21 interferon products: 5 recombinant human interferon 2a for injection, 2 recombinant human interferon 1b for injection, 11 recombinant human interferon 2b for injection, 1 pegylated interferon -2b injection, and 1 recombinant cytokine gene-derived protein injection. These approvals involved 19 manufacturers, with Xiamen Amoytop Biotech being the only domestic producer of pegylated interferon -2b injection.

During 2012-2017, CFDA approved 47 nucleos(t)ide analog products: 6 lamivudine, 20 adefovir, 13 entecavir, 1 telbivudine, and 6 tenofovir (tenofovir disoproxil fumarate) formulations. Over 40 companies manufacture these agents, including GlaxoSmithKline, Fujian Cosunter Pharmaceutical, Chia Tai Tianqing Pharmaceutical, and Beijing Novartis [Figure 1: see original paper].

2.3 Market Situation

According to MENET data, China' s liver disease drug market has reached 60 billion RMB, maintaining over 15% annual growth in 2016 and 2017, with projections to reach 100 billion RMB by 2020. Due to interferons' weaker and slower HBV DNA suppression, injectable administration, greater side effects, and narrower indications compared to nucleos(t)ide analogs, nucleos(t)ide analogs account for approximately 80% of China' s hepatitis B drug market and have become the mainstream treatment. Entecavir leads the market, capturing over 50% market share in 2015-2016 with continued growth. Since its inclusion in the National Reimbursement Drug List in 2009, entecavir has become the dominant product in China' s nucleos(t)ide analog market. Telbivudine, lamivudine, and adefovir dipivoxil maintain some market share but show declining sales trends. Tenofovir held a small but growing market share in 2015-2016. The 2017 EASL hepatitis B guidelines recommend entecavir, tenofovir, and tenofovir alafenamide as first-line monotherapy options. Despite its currently modest market share, tenofovir' s prospects as a first-line agent are promising, with domestic companies such as Chengdu Brilliant Pharmaceutical, Fujian Cosunter Pharmaceutical, Qilu Pharmaceutical, Anhui Baker Biotechnology, and Chia Tai Tianqing actively developing generics [Figure 2: see original paper].

As shown in [Figure 3: see original paper], the top 10 enterprises in urban retail sales of anti-HBV drugs accounted for 91.8% of total retail market share in 2016,

demonstrating high market concentration. Among the top 10, six were domestic companies and four were foreign enterprises. Chia Tai Tianqing ranked first with 28.1% market share, driven by its core product Run Entecavir Dispersible Tablets, which achieved 3.5 billion HKD in sales in 2016. Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Gilead ranked second through fifth, respectively. GlaxoSmithKline' s original lamivudine and adefovir dipivoxil tablets have faced intense generic competition since patent expiry.

2.4 R&D Landscape

Although China' s novel anti-HBV drug R&D lags behind Europe and the United States, domestic innovation policies have encouraged over 20 companies to strengthen R&D efforts with notable achievements. Fourteen companies are developing interferon products, with several long-acting interferons in clinical trials or under clinical application, including pegylated interferon 2a injections from Xiamen Amoytop and Chia Tai Tianqing, and pegylated interferon 2b injections from Anhui Anke Biotechnology and Changchun Hiber. Currently, no domestic generic version of pegylated interferon 2a exists.

Amdoxovir and Mivircavir are in Phase II clinical trials under China' s Major New Drug Innovation program. Mivircavir, like entecavir, is a deoxyguanosine analog with promising efficacy and low resistance potential, suggesting strong market potential. Hepalutide binds to the HBV hepatocyte infection receptor NTCP (sodium taurocholate cotransporting polypeptide) to block HBV infection, enabling healthy hepatocytes to gradually replace infected cells and improving treatment efficacy. Dongguan Sunshine' s Mofetil Mesylate (GLS4) is China' s only domestically developed capsid protein inhibitor in clinical trials—a new-generation dihydropyrimidine with independent intellectual property rights demonstrating favorable anti-HBV effects, currently in Phase II/III clinical trials .

3 Policy Recommendations for China' s Anti-HBV Drug Development

Analysis of domestic and international anti-HBV drug markets reveals growing global emphasis on hepatitis B treatment, particularly in China where it represents a critical public health priority. The China Viral Hepatitis Prevention and Treatment Plan (2017-2020) mandates priority review pathways for antiviral drugs with significant efficacy and urges inclusion of more hepatitis drugs in the National Essential Medicines List. Domestic enterprises have surpassed foreign companies in urban retail market share, and anti-HBV drugs covered by medical insurance account for substantial market share. However, China' s novel drug R&D capabilities still lag behind Europe and the United States, and medical insurance coverage requires further improvement.

To advance anti-HBV drug development, three key measures are recommended. First, continue improving medical insurance policies for anti-HBV drugs. Given

the lengthy treatment courses and high costs of highly effective, low-resistance agents, many remain uncovered by insurance, and antiviral drugs are not included in outpatient reimbursement in many provinces, preventing patients from maintaining long-term therapy. Recommendations include further price reductions, increased reimbursement ratios, and expanded insurance coverage for outpatient anti-HBV treatment. Second, deploy and implement major hepatitis B R&D programs. As a country with high HBV prevalence, China should leverage its abundant patient resources to support basic and original research, strengthen fundamental data collection, and accelerate domestic novel anti-HBV drug development. Third, promote deep integration of industry, academia, and research. Anti-HBV drug manufacturers should enhance innovation capacity and R&D investment, while universities and research institutes should adopt market-oriented approaches to serve enterprise needs, addressing gaps in anti-HBV drug development through diverse collaboration mechanisms such as secondments, part-time appointments, and joint projects.

Viral hepatitis B treatment represents a worldwide public health challenge. While no ideal curative therapy currently exists, recent progress with interferons and nucleos(t)ide analogs has achieved encouraging results. Tenofovir and entecavir, recommended as first-line high-barrier-to-resistance nucleos(t)ide analogs, have captured substantial market share globally, with numerous novel anti-HBV agents under development. As a major HBV-endemic country, China has included entecavir and tenofovir in its National Reimbursement Drug List, with CFDA approving 47 nucleos(t)ide analog products during 2012-2017. Domestic companies such as Dongguan Sunshine and Shanghai Hepro Biotechnology are accelerating development of novel anti-HBV agents. As scientific understanding of HBV replication and virus-host interactions deepens, new targets and antiviral agents continue to emerge, offering promise to ultimately overcome this major public health threat and advance the development of the health industry.

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Note: Figure translations are in progress. See original paper for figures.