Original Article

Nucleot(s)ide Analogs for Chronic Hepatitis Virus Therapy: A Global Bibliometric Analysis (1986-2022)

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ABSTRACT

Objectives

This study aimed to analyze the global profile of the nucleotide/nucleoside analogs (NAs) for chronic hepatitis virus therapy-related research.

Background

NAs, which closely resemble the structure of naturally occurring nucleotides/nucleosides, function by disrupting the elongation of the nascent DNA strand. These compounds are considered safe and well-tolerated, as they specifically target viral, but not human, polymerases involved in DNA replication. NAs are crucial in treating viral infections, including hepatitis, and are widely used due to their efficacy and safety. However, a study about trends in NAs for chronic hepatitis therapy-related research was never reported before.

Methods

The NAs for chronic hepatitis therapy-related research bibliometric analysis was performed on articles indexed in the Scopus database from 1986 to 2022.

Results

The total number of articles published worldwide is 2,341 documents, with an annual average of 65 documents. The United States generated the most articles (n = 486), followed by China (n = 454), France (n = 191), and Italy (n = 179). Since 1992, the number of publications has increased dramatically worldwide. Globally, liver cell carcinoma, antiviral therapy, hepatitis B (e) antigen, and alanine aminotransferase are becoming hot research topics in the field.

Conclusions

This study provides a unique composite picture of NAs for chronic hepatitis therapy-related research worldwide and evaluates research productivity from 1986 to 2022. This finding suggests that the prospects for interventions in chronic hepatitis remain promising.

INTRODUCTION

A viral infection called hepatitis is a condition of the liver that results in inflammation of the liver tissue and can even be fatal[1]. Numerous viruses, including the hepatitis A, B, C, D, and E viruses, can contribute to this illness. A number of symptoms, such as fatigue, fever, abdominal pain, jaundice, and black urine, can be caused by the dangerous illness hepatitis[1]. The most prevalent hepatitis cases, nevertheless, are hepatitis B and C, which afflict 354 million people globally and, among other hepatitis kinds, cause serious liver disease[1,2]. Hepatitis B instances that progress to cirrhosis or hepatocellular cancer were documented in 2019 in about 820,000 cases, according to the World Health Organization

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(WHO)[3]. Hepatocytes are infected by the Hepatitis B Virus (HBV), which then induces oxidative stress in Kupffer cells to encourage cell activation. Cirrhosis is caused by chronic activation[4].

Hepatitis B's global spread, on the other hand, is a significant issue. If the mother has already had hepatitis B, it is possible for her to pass the virus vertically to the unborn child during pregnancy and childbirth. Hepatitis B transmission through natality is now more likely as a result[5,7]. About 95% of newborns with HBV infection persist, and 90% of perinatal patients with HBV infection develop chronic infection[4,6].

Several risk factors can increase the risk of hepatitis B development including age, gender, occupation, alcohol consumption, blood transfusion, surgery and family history of disease, tattoo application, and vaccination[8–12]. A combination of nucleotide analogs such as entecavir and pegylated (PEG)-INF has the potential factors to be an antiviral with a 71% success rate in therapeutic attempts of chronic hepatitis B patients4[13] (Table A.1.). Nucleotide analogs are composed of phosphate groups, sugars, and nucleic acid analogs. On the enzymes that anti-cancer and anti-viral chemotherapeutics target, nucleotide analogs operate as DNA and RNA polymerases[14,15]. Nucleoside analogs, on the other hand, are sugar and nucleic acid analogs. Analogs of nucleosides are incorporated into both DNA and RNA and mimic natural nucleosides. Nucleoside analogs are effective antiviral and anticancer agents because of this circumstance[14,16].

The global application of nucleotide/nucleoside analogs (NAs) for hepatitis B treatment has also increased, and effectiveness has been evaluated throughout number of studies. Therefore, a bibliometric analysis is necessary to comprehend the global research profile on the state of the art in NAs for chronic hepatitis therapy. In addition, the bibliometric analysis has been used to evaluate the global profile of various topics, such as monkeypox, chikungunya, DNA barcoding, snake venom, and insecticides[17–21]. To provide a basis for long-term research development, a bibliometric analysis was conducted on articles related to nucleotide analog therapy for chronic hepatitis published between 1986 and 2022. The analysis aimed to provide global profile of related literature, which can be beneficial for future research studies.

METHOD AND MATERIALS

The Scopus database was utilized to gather research articles on NAs for hepatitis therapy published between 1986-2022. Scopus, a leading source for bibliometric analysis across various fields, served as the primary data source for the study. In February 2023, a bibliometric filter was created and applied to the Scopus database using key terms such as (TITLE-ABS-KEY (chronic AND hepatitis AND treatment) OR TITLE-ABS-KEY (chronic AND hepatitis AND therapy) AND TITLE-ABS-KEY (nucleotide AND analog AND therapy) OR TITLE-ABS-KEY (nucleoside AND analog AND therapy)). Using VOSviewer software[22], data from Scopus was analyzed to determine key bibliometric indicators, including publication year, institutions, countries, journal titles, citations, and key terms. The results of the analysis provided an understanding of the research trends, patterns, and prominent contributors to the field of NAs for hepatitis therapy.

RESULTS:

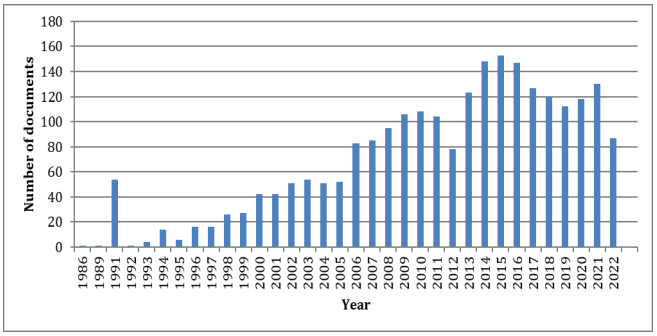

Figure 1. Publication profile of NAs for chronic hepatitis therapy during the years 1986-2022.

Between 1986 and 2022, a total of 2,341 studies were conducted on NAs for the treatment of chronic hepatitis, with an average of 65 studies per year. Figure 1 illustrates a steady growth in the global publication trend over the years. Notably, the highest number of publications (n=153) was recorded in 2015.

Table 1. The top articles of NAs for chronic hepatitis therapy-related research.

SCR	Title	Year	Authors	Journal	Volume	Citation
1	"Peginterferon Alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B"	2004	Marcellin, P., Lau, G.K.K., Bonino, F., (...), Button, P., Pluck, N.[23]	New England Journal of Medicine	351(12), pp. 1206-1217	1055
2	"Hepatitis B virus infection"	2009	Liaw, Y.-F., Chu, C.-M. [24]	The Lancet	373(9663), pp. 582-592	1019
3	"Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection"	2000	Sulkowski, M.S., Thomas, D.L., Chaisson, R.E., Moore, R.D. [25]	JAMA	283(1), pp. 74-80	892
4	"Viral dynamics in hepatitis B virus infection"	1996	Nowak, M.A., Bonhoeffer, S., Hill, A.M., (...), Thomas, H.C., Mcdade, H. [26]	Proceedings of the National Academy of Sciences of the United States of America	93(9), pp. 4398-4402	843
5	"Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases"	2013	Jordheim, L.P., Durantel, D., Zoulim, F., Dumontet, C. [27]	Nature Reviews Drug Discovery	12(6), pp. 447-464	802
6	"Identification and characterization of mutations in hepatitis B virus resistant to lamivudine"	1998	Allen, M.I., Deslauriers, M., Webster Andrews, C., (...), Brown, N., Condreay, L.D.[28]	Hepatology	27(6), pp. 1670-1677	782
7	"Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B"	2010	Chang, T.-T., Liaw, Y.-F., Wu, S.-S., (...), Beebe, S., Kreter, B. [29]	Hepatology	52(3), pp. 886-893	766
8	"Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guidelines proposed by the Japan society of hepatology (JSH) 2010 updated version"	2011	Kudo, M., Izumi, N., Kokudo, N., (...), Kojiro, M., Makuuchi, M. [30]	Digestive Diseases	29(3), pp. 339-364	639
9	"Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients with Advanced Liver Disease"	2015	Charlton, M., Everson, G.T., Flamm, S.L., (...), Reddy, K.R., Afdhal, N.[31]	Gastroenterology	149(3), pp. 649-659	635
10	"Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma"	2013	Arzumanyan, A., Reis, H.M.G.P.V., Feitelson, M.A.[32]	Nature Reviews Cancer	13(2), pp. 123-135	634

Table 1 presents the top ten articles on NAs research for chronic hepatitis therapy. Citation numbers, which reflects the number of studies referencing a particular article, was used to identify these top articles. The higher the citation numbers, the more studies refer to the article. The article titled "Peginterferon Alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B" had the highest cite score of 1055 among the top ten articles.

Table 2. The institutions with the most publications.

SCR[a]	Institution	Country	Number of documents (%)
1	Inserm	France	117 (4.99)
2	The University of Hong Kong	Hong Kong	68 (2.90)
3	Erasmus MC	Netherlands	61 (2.60)
4	Queen Mary Hospital Hong Kong	Hong Kong	57 (2.43)
5	Chang Gung Memorial Hospital	Taiwan	49 (2.09)
6	Southern Medical University	China	48 (2.05)
7	Ospedale Maggiore Policlinico Milano	Italy	47 (2.01)
8	National Taiwan University Hospital	Taiwan	47 (2.01)
9	Chinese University of Hong Kong	Hong Kong	46 (1.96)
10	Università degli Studi di Milano	Italy	46 (1.96)

[a]SCR: standard competition ranking

Table 2 lists institutions with a large number of publications related to NAs therapy for chronic hepatitis. Inserm, which is based in France, has the highest number of publications with 117 documents, while Chinese University of Hong Kong, which is based in Hong Kong, and Università degli Studi di Milano, which is based in Italy, have the lowest number of publications with 46 documents.

Table 3. The top ten journals for NAs for chronic hepatitis therapy.

SCR[a]	Name of Journal	Number of documents (%)	SJR[b] 2021	Cite Score[c] 2021
1	Journal of Viral Hepatitis	74 (3.16)	1.034	6.1
2	Liver International	74 (3.16)	2.064	11.2
3	Journal of Hepatology	73 (3.11)	7.351	39.2
4	Hepatology	63 (2.69)	5.235	25.8
5	Antiviral Therapy	57 (2.43)	0.835	5.1
6	World Journal of Gastroenterology	50 (2.13)	1.229	8.1
7	Antiviral Research	49 (2.09)	2.213	15.0
8	Alimentary Pharmacology and Therapeutics	47 (2.01)	2.85	15.2
9	Journal of Gastroenterology and Hepatology Australia	45 (1.92)	1.063	6.0
10	Hepatology Research	40 (1.70)	1.121	7.8

[a]SCR: Standard competition ranking. [b]SJR: SCImago Journal Rank calculates the serial's weighted citations. Citation weighting is influenced by the citing series' status (SJR) and subject area. [c]Cite Score: CiteScore calculates the typical number of citations per serially released document.

Tabel 3 lists the top ten journals with the highest number of publications related to NAs therapy for chronic hepatitis. The journal with the most papers is Journal of Viral Hepatitis and Liver International, which has 74 documents, while Hepatology Research has the Lowest number of documents.

Table 4. The top ten countries in the publication of NAs for chronic hepatitis therapy.

SCR[a]	Country	Number of documents (%)	Number of Collaborating Countries[b]
1	United States	486 (20.76)	34
2	China	454 (19.39)	30
3	France	191 (8.15)	32
4	Italy	179 (7.64)	28
5	Germany	172 (7.34)	33
6	Japan	170 (7.26)	25
7	Taiwan	134 (5.72)	28
8	Hong Kong	115 (4.91)	28
9	United Kingdom	110 (4.69)	30
10	Spain	101 (4.31)	29

[a]SCR: standard competition ranking. [b]Number of collaborating countries with a minimum threshold of 50 documents.

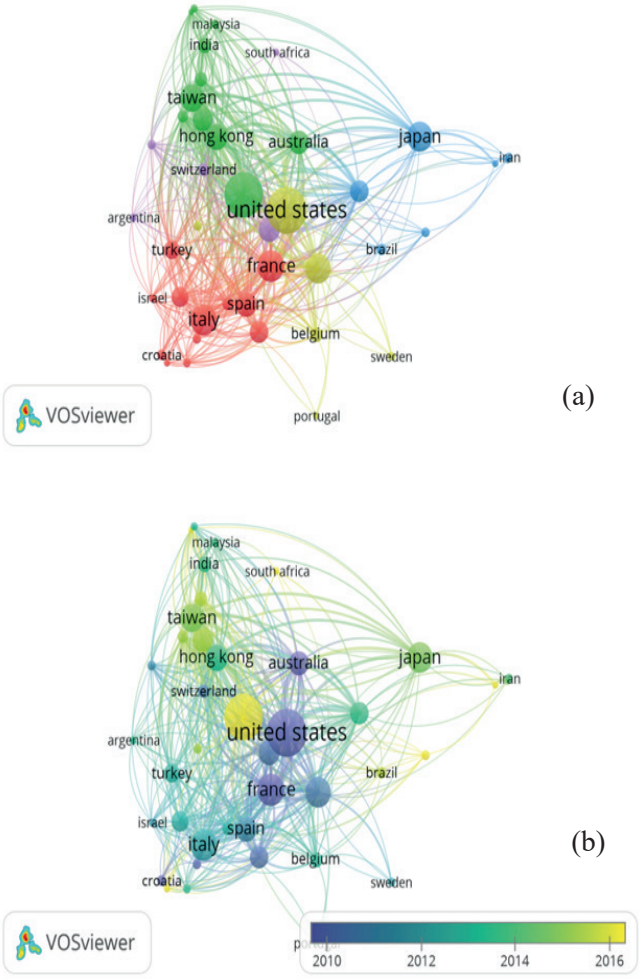

Figure 2. VOSviewer mapping of collaboration countries. (a) network visualization; (b) overlay visualization. The link's length reveals the degree of connection to at least five documents.

Between 1986 and 2022, a total of 41 countries published research on NAs for chronic hepatitis therapy. Figure 2 demonstrates the number of clusters formed after visualizing the data with VOSviewer. Five clusters are observed, each corresponding to a unique group. The growing clusters are color-coded as red, yellow, green, blue, and purple in Figure 2a. Figure 2b shows a cluster that ranges from purple to yellow, representing publications from 2010 to 2016. This cluster transition reflects the shift from old to new publications. Table 4 presents the top ten countries in terms of the number of publications, with the United States having the highest number (n=486) and Spain having the lowest (n=101).

Table 5. Top ten authors in NAs for chronic hepatitis therapy research.

SCR[a]	Author	Number of documents (%)	Scopus ID[b]	H-index[c]
1	Zoulim, F.	72 (3.07)	7006912131	**94**
2	Yuen, M.F.	47 (2.01)	7102031955	**84**
3	Janssen, H.L.A.	46 (1.96)	56489785600	**95**
4	Marcellin, P.	41 (1.75)	7102079502	**120**
5	Lai, C.L.	35 (1.49)	7403086396	**101**
6	Lampertico, P.	32 (1.36)	7006770607	**58**
7	Seto, W.K.	30 (1.28)	56404308000	**47**
8	Kao, J.H.	29 (1.23)	7201375585	**76**
9	Chan, H.L.Y.	27 (1.15)	25722700100	**101**
10	Locarnini, S.	27 (1.15)	35953095500	**87**

[a]SCR: standard competition ranking. [b]Scopus ID: The Scopus Author Identifier is a special number that associates writers with collections of documents. [c]H-index: The productivity and citation effect of the publications are gauged by the author-level indicator.

Figure 3 showcases the number of author clusters visualized using VOSviewer. There are five color-coded clusters - red, yellow, green, blue, and purple - as shown in Figure 3a. Figure 3b displays a cluster that ranges from purple to yellow, representing publications from 2008 to 2018. This cluster transition demonstrates the shift from old to new publications. Table 5 presents the top ten authors who contributed to studies on NAs therapy for chronic hepatitis. Zoulim, F. had the highest number of publications (n=72), followed by Yuen, M.F. (n=47) and Janssen, H.L.A (n=46).

Figure 4 illustrates the various themes or keywords used in research on nucleotide analog therapy for chronic hepatitis . After analyzing with VOSviewer, 30 keywords were grouped into two clusters. The growing clusters are represented by the colors red and green (Figure 4a). Figure 4b displays a cluster with shades of color ranging from purple to yellow, representing publications from 2010 to 2013 transitioning from old to new. Figure 4c shows the density of research on nucleotide analogs for chronic hepatitis therapy, with the number of studies increasing as brighter colors appear. The commonly used keywords in nucleotide analog therapy research for chronic hepatitis include antiviral agents, chronic hepatitis B, and lamivudine.

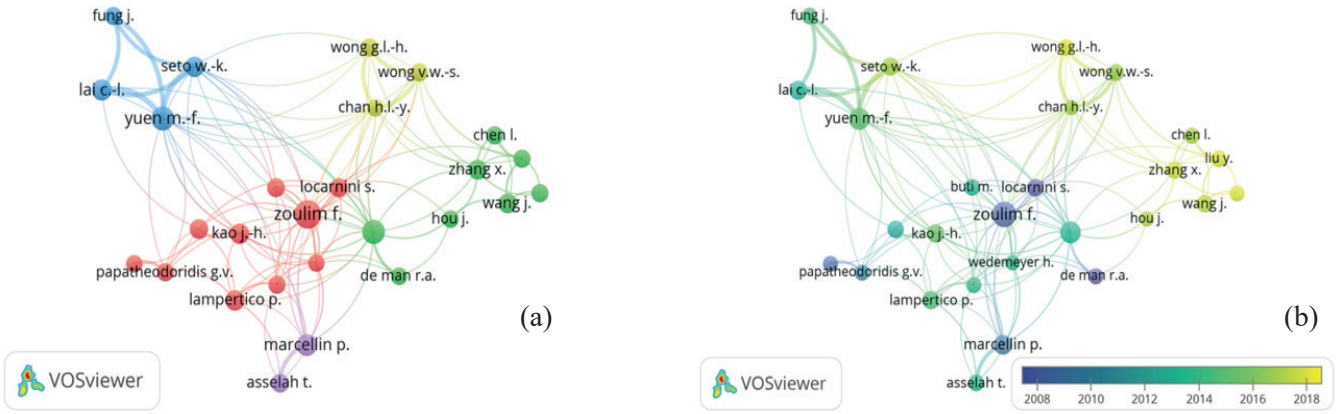

Figure 3. VOSviewer mapping of authors. (a) network visualization; (b) overlay visualization. The length of the link reveals the degree of the relationship, and a minimum of 20 documents must be written by each author.

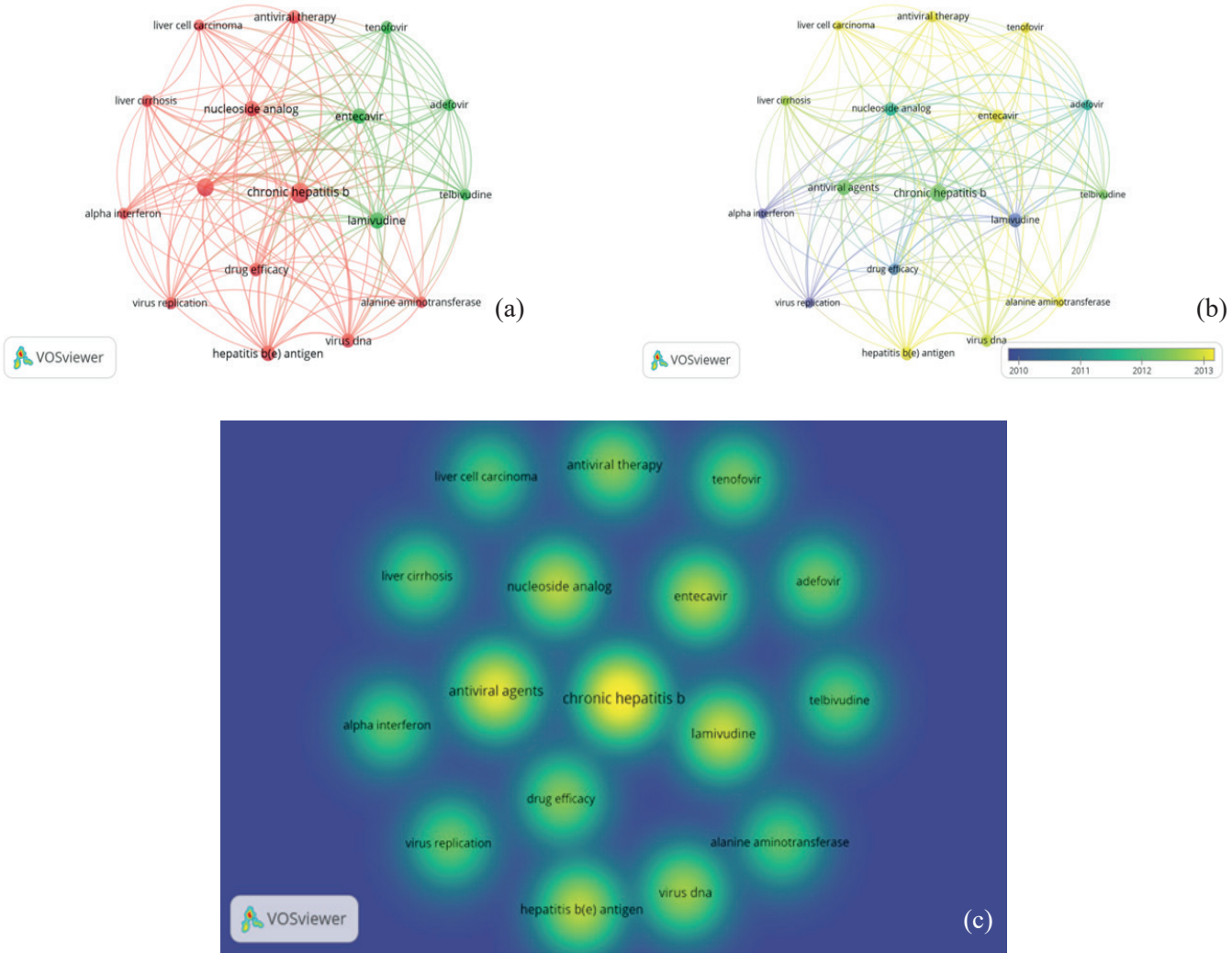

Figure 4. VOSviewer mapping of keywords related to NAs for chronic hepatitis therapy. (a) network visualization; (b) overlay visualization; (c) density visualization. The length of the link indicates the degree of relationship with 500 occurrences.

DISCUSSIONS

Hepatitis B infection has been known about for a while, and it was even connected to hepatocellular cancer in 1970. As a result, many investigations were conducted in the 1980s to discover and comprehend the traits of the hepatitis B virus using genome sequencing[33]. Additionally, that year saw the creation of vaccinations in an effort to lower the incidence of hepatitis B. This was accomplished by developing vaccinations generated from plasma, and in 1986, work on developing vaccines based on recombinant HBV DNA began[34]. Due to the fact that hepatitis B vaccinations have been available since 1986, there has been an increase in disease screening. Additionally, this has led to a sharp rise in the quantity of research articles released in 2015.

The development of NAs for chronic hepatitis therapy has been ongoing for the past 36 years, with recent articles serving as resources for new research. One such article, "Peginterferon Alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B," published in the New England Journal of Medicine in 2004, has been cited as a source of inspiration and has contributed significantly to the study of NAs for chronic hepatitis therapy[23]. This article has gained significant attention with 1055 citations, indicating its importance in the field of nucleotide analog research for chronic hepatitis. Furthermore, the growth of research in this field is reflected in the increasing number of papers being published in relevant journals such as the Journal of Viral Hepatitis and Liver International, which have a combined total of 148 documents. The Journal of Viral Hepatitis first published in 1994, under the title of "Treatment of Chronic Hepatitis B," and has continued to serve as a platform for sharing the latest research findings and advancements in the field[35]. Meanwhile in 2003, a clinical and technical report titled "MARS therapy in critically ill patients with advanced malignancy" was published in Liver International journal[36]. Furthermore, several authors have been prolific in their research on NAs for chronic hepatitis, including F. Zoulim, who has published 72 documents.

Between 1986 and 2022, the United States had the highest number of publications on NAs for chronic hepatitis with 486 publications, while Inserm in France was the most productive institutions with 117 documents. Notably, both countries have made significant contributions to the fight against hepatitis B, having been where the virus was first discovered[34]. Additionally, the increasing prevalence of hepatitis B in the United States has driven research efforts. The estimated number of hepatitis B cases in the United States is around 1.59 million, therefore there is still much work to be done to combat this disease[37]. In addition, certain research areas, such as liver cell carcinoma, antiviral therapy, hepatitis B (e) antigen and alanine aminotransferase predicted to be popular topics for investigating the chronic hepatitis.

Antiviral medications are commonly used to treat hepatitis B, with two main types being immunomodulatory agents and oral NAs[38]. Lamivudine is an example of an NA that can be used to treat the virus[38]. Nucleoside analogs have the potential to enhance virus replication and improve human health[39]. The mechanism of action of NAs involves inhibiting the interaction of the HBV virus with its natural substrate, preventing it from binding to cell membranes and entering host cells[40]. Moreover, NAs can aid in the transcription, translation, and enzymatic processes required for the replication of the HBV virus[38]. Although NAs are generally safe for use in patients with HBV, prolonged use can inhibit their growth and lead to toxicity[41]. Therefore, there is a need to develop hepatitis B treatment methods that have fewer adverse effects.

CONCLUSION

Since 1986, there has been a rise in global interest in researching NAs for the treatment of chronic hepatitis. Various countries and institutions have participated in this development, with the hope that it will provide insights into strategies for managing hepatitis in the future.

Table A.1. NAs which have been used in chronic hepatitis therapy

NAs	Structure	Activity	References
Nucleoside analog			
Adefovir dipivoxil	An analog of adenosine monophosphate	DNA polymerase and reverse transcriptase inhibition	[42], [43]
Tenofovir	An acyclic phosphonate of nucleosides	Block the HBV DNA polymerase's natural substrate deoxyadenosine 5′-triphosphate and serve as a chain terminator.	[44]–[46]
Nucleotide analog			
Lamivudine	An analog of cytidine	Inhibit and surpress HBV DNA synthesis by incorporating 3TC-TP into viral DNA	[40], [44], [47], [48]
Entecavir	A guanosine carboxylic analog	Suppresses HBV replication by inhibiting HBV DNA polymerase priming, reverse transcription of the negative-strand HBV DNA, and synthesis of the positive-strand HBV DNA.	[43], [49], [50]
Telbivudine	An analog of thymidine	Competing with Thymidine 5′-triphosphate to inhibits HBV DNA polymerase	[38], [44]

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