CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Clin Exp Vaccine Res 2024;13:21-27
https://doi.org/10.7774/cevr.2024.13.1.21
pISSN 2287-3651 • eISSN 2287-366X

Current development of therapeutic vaccines for the treatment of chronic infectious diseases

Pil-Gu Park[1,2,*], Munazza Fatima[1,2,*], Timothy An[2], Ye-Eun Moon[2,3], Seungkyun Woo[2,3], Hyewon Youn[4,5], Kee-Jong Hong[1,3]

[1]Department of Microbiology, Gachon University College of Medicine, Incheon; [2]Lee Gil Ya Cancer and Diabetes Institute, Gachon University, Incheon; [3]Department of Health Sciences and Technology, GAIHST, Gachon University, Incheon; [4]Department of Nuclear Medicine, Cancer Imaging Center, Seoul National University Hospital, Seoul; [5]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

Received: December 29, 2023
Accepted: December 29, 2023

Corresponding author: Kee-Jong Hong, PhD
Department of Microbiology, Gachon University College of Medicine, 155 Gaetbeol-ro, Yeonsu-gu, Incheon 21999, Korea
Tel: +82-32-899-6064, Fax: +82-32-899-6039
E-mail: calcium@gachon.ac.kr

*These authors contributed equally to this work as the first author.

No potential conflict of interest relevant to this article was reported.

This research was supported by grants (23202MFDS145 & RS-2023-00217026) from Ministry of Food and Drug Safety in 2023.

Chronic infectious diseases refer to diseases that require a long period of time from onset to cure or death, the use of therapeutic vaccines has recently emerged to eradicate diseases. Currently, clinical research is underway to develop therapeutic vaccines for chronic infectious diseases based on various vaccine formulations, and the recent success of the messenger RNA vaccine platform and efforts to apply it to therapeutic vaccines are having a positive impact on conquering chronic infectious diseases. However, since research on the development of therapeutic vaccines is still relatively lacking compared to prophylactic vaccines, there is a need to focus more on the development of therapeutic vaccines to overcome threats to human health caused by chronic infectious diseases. In order to accelerate the development of therapeutic vaccines for chronic infectious diseases in the future, it is necessary to establish a clear concept of therapeutic vaccines suitable for the characteristics of each chronic infectious disease, as well as standardize vaccine effectiveness evaluation methods, secure standards/reference materials, and simplify the vaccine approval procedure.

Keywords: Chronic infectious disease, Therapeutic vaccine, Clinical trials

Introduction

Although many infectious diseases are acute, most of the deaths and disease caused by infections worldwide today result from chronic infections [1]. Many people around the world are suffering from chronic infectious diseases and the number is increasing, so the development of effective response strategies for chronic infectious diseases is urgent. Because chronic infectious diseases have the potential for latent infection and recurrence, it is especially important to develop treatments for the large number of already infected carriers rather than prevention for healthy people. Chronic infectious diseases are often difficult to cure with a single treatment due to the nature of the causative pathogen continuously exists in the body, and long-term treatment may lead to the development of mutant strains resistant to the treatment. In fact, there are reports of the occurrence of multidrug-resistant pathogens in many chronic infectious diseases [2-4], which suggests the limitations of drug therapy in the treatment of chronic infectious diseases.

In this situation, approaches using "therapeutic" vaccines as a treatment strategy for chronic infectious diseases have recently received attention [5]. The application of "therapeutic" vaccines utilized the body's immune mechanism to alleviate symptoms caused by infection or prevent reactivation of infected pathogens, so therapeutic effects

can be expected without concerns about drug resistance or side effects. Therefore, it is considered that using therapeutic vaccines to respond to chronic infectious diseases will overcome the limitations of existing drug treatments and enable more efficient treatment. Accordingly, in order to prepare effective response strategies for chronic infectious diseases in the future, it is necessary to accurately understand the research and development trends of therapeutic vaccines. In this review, we examine the current status of therapeutic vaccine development for each major chronic infectious disease with high clinical demand, and based on this, we will consider current issues and improvement strategies to solve them.

Human Papilloma Virus

Human papilloma virus (HPV) is known to infect mucous squamous cells or the skin and cause warts or papillomas near the genitals, or malignant tumors in the uterus, anus, and genitals [6]. It is estimated that 4.5% of all cancers worldwide are related to HPV infection, and approximately 80% of them are known to be cervical cancer [7].

Gardasil (Merck & Co. Inc., Rahway, NJ, USA) and Cervarix (GlaxoSmithKline, London, UK) are currently being used as HPV preventive vaccines, but these vaccines are known to have little efficacy in treating patients already infected with the virus [8], and no vaccine has yet been approved for treatment. It is well known that the E6 and E7 proteins expressed during latent HPV infection induce tumorigenesis by suppressing the activities of p53 and pRB, respectively [9]. Accordingly, oncoproteins E6 and E7 are considered the two most important target antigens for HPV therapeutic vaccines and are widely used as targets for most HPV therapeutic vaccines in development. Currently, efforts are being made to develop a vaccine for the treatment of cervical cancers caused by HPV infection based on various vaccine formulations (Table 1).

Epstein-Barr Virus

Epstein-Barr virus (EBV) infection is one of the most common infections in humans and is mainly spread through saliva. Most infected patients do not show any special symptoms, but in immunocompromised patients, it can cause malignant cancers such as lymphoma, stomach cancer, and nasopharyngeal cancer. Therefore, the International Agency for Research on Cancer classifies this virus as Group 1 risk factor that is clearly carcinogenic to humans [10]. As of 2017, approximately

Table 1. Current status of clinical trials for therapeutic vaccines targeting HPV

Vaccine	Antigen	Formulation	Clinical stage	ID[a)]
ADXS11-001	HPV16 E7	Bacterial vectored vaccine	Phase 2	NCT02291055
TA-HPV	HPV16/18 E6, E7	Viral vectored vaccine	Phase 2	NCT05799144
ProCervix	HPV16/18 E7	Recombinant protein	Phase 2	NCT01957878
ISA101b	HPV16 E6, E7	Recombinant protein	Phase 2	NCT02128126
SGN-00101	HPV16 E7	Recombinant protein	Phase 2	NCT00054041
pNGVL4a-Sig/E7(detox)/HSP70	HPV16 E7	DNA vaccine	Phase 1	NCT00788164
INO-3112	HPV16/18 E6, E7	DNA vaccine	Phase 2	NCT03162224
GX-188E	HPV16/18 E6, E7	DNA vaccine	Phase 2	NCT03444376
BNT113	HPV16 E6, E7	mRNA vaccine	Phase 2	NCT04534205

HPV, human papilloma virus; mRNA, messenger RNA.
[a)]ClinicalTrials.gov registration number of representative clinical study.

Table 2. Current status of clinical trials for therapeutic vaccines targeting EBV

Vaccine	Antigen	Formulation	Clinical stage	ID[a)]
Ad5-EBV-LMP2	LMP2	Peptide vaccine	Phase 1	NCT00078494
MVA-EL	EBNA1, LMP2	Viral vectored vaccine	Phase 1	NCT01147991
MVA-EBNA1/LMP2	EBNA1, LMP2	Viral vectored vaccine	Phase 2	NCT01094405
LPX-mLMP2	LMP2	mRNA vaccine	Phase 1	NCT05714748
mRNA-1195	Not disclosed	mRNA vaccine	Phase 1	NCT05831111

EBV, Epstein-Barr virus; mRNA, messenger RNA.
[a)]ClinicalTrials.gov registration number of representative clinical study.

 https://doi.org/10.7774/cevr.2024.13.1.21

265,000 cases (18%) and 164,000 deaths (17%) were reported worldwide due to EBV-related lymphoma, Hodgkin's lymphoma, nasopharyngeal cancer, and stomach cancer [11].

It is well known that latent proteins, such as EBNA1, LMP1, and LMP2, expressed during EBV latent infection, play an important role in the carcinogenesis of EBV-related tumors [12]. Accordingly, vaccines for the treatment of EBV chronic infection currently under research and development mainly uses EBV latent proteins as target antigens, and various formulations of vaccine candidates based on these antigens are currently undergoing early clinical research (Table 2).

Cytomegalovirus

Cytomegalovirus (CMV) mainly infects humans and non-human primates as hosts, and commonly infects people of all ages. Once infected, it remains latent for life and it is reactivated when the host's immunity decreased, causing various symptoms [13]. It can infect most digestive organs, including the esophagus, stomach, liver, pancreas, and large intestine, and when it progresses to a serious disease, it causes ulcers, hepatitis, intestinal obstruction, and colitis [14]. Additionally, pneumonia caused by lung infection with CMV can be life-threatening, and retinitis caused by eye infection with CMV can sometimes lead to blindness [15].

Since chronic infection with CMV rarely shows symptoms during latent infection, re-infection and re-activation of the virus cause clinically important problems, so the development of therapeutic vaccines mainly targeting envelope proteins that can neutralize virus particles is currently in progress (Table 3).

Varicella Zoster Virus

Varicella zoster virus (VZV) is a pathogen that causes two diseases depending on the type of infection. Primary infection caused by VZV appears as varicella (chickenpox), but the infected virus remains latent in the dorsal root ganglia and is likely to reactivated mainly in immunocompromised patients or those in their 50s or older, resulting in shingles (herpes zoster) [16]. The annual incidence of shingles around the world is 1.2 to 3.4 cases per 1,000 people, and is known to exceed 10 cases per 1,000 people over the age of 75 years. The lifetime risk of developing shingles is estimated to be 10%–20% [17,18]. Clinical symptoms of shingles appear over a broad spectrum, from pain without rash to mild rash to severe rash with dissemination. In immunocompromised patients, it can cause serious neurological diseases such as outer retina necrosis that causes vision loss, gastrointestinal diseases, and angiopathy [19]. In addition, postherpetic neuralgia (PHN) is a representative aftereffect of shingles and is a neuropathic pain syndrome that occurs about a month after the onset of shingles. PHN is often severe and the incidence is known to increase with age [20].

Varicella and shingles are caused by the infection with the same pathogen, so basically, the same vaccine can be used for each infection. However, in order to suppress the viral recurrence that causes shingles, a much higher dose of antigen must be used than to prevent initial infection. Therefore, it is necessary to distinguish between varicella and shingles vaccine. The currently approved shingles vaccine (treatment vaccine) shows a dose level about 14 times higher than the shingles vaccine (preventive vaccine) [21].

Currently, two live-attenuated vaccine (ZOSTAVAX; Merck & Co. Inc. and SKYZoster; SK Bioscience, Seongnam, Korea) and a recombinant vaccine (SHINGRIX; GlaxoSmithKline) are most widely used as approved shingles vaccine. Due to the safety issue, the demand for the use of subunit vaccines such as SHINGRIX is increasing, and additional shingles vaccines using various subunit formulations are under way in clinical trials (Table 4).

Table 3. Current status of clinical trials for therapeutic vaccines targeting CMV

Vaccine	Antigen	Formulation	Clinical stage	ID[a]
TransVax (ASP0113)	gB, pp65	DNA vaccine	Phase 3	NCT01877655
CMV gB/MF59	gB	Recombinant protein	Phase 2	NCT00125502
vCP260 (ALVAC-pp65)	pp65	Viral vectored vaccine	Phase 2	NCT00353977
CMV-MVA Triplex	pp65, IE1, IE2	Viral vectored vaccine	Phase 2	NCT06059391
mRNA-1647	gB, PC	mRNA vaccine	Phase 3	NCT05085366

CMV, cytomegalovirus; mRNA, messenger RNA.
[a]ClinicalTrials.gov registration number of representative clinical study.

Herpes Simplex Virus

Herpes simplex virus (HSV) mainly infects the skin and mucous membranes, and is divided into type 1 (HSV-1) and type 2 (HSV-2). Therefore, HSV-1 is generally associated with oral and eye diseases but the ratio of sexually transmitted diseases due to HSV-1 tends to increase [22]. On the other hand, HSV-2 is one of the world's most widespread sexually transmitted diseases, with approximately 23 million new infections reported to occur every year [23]. According to World Health Organization (WHO), it is estimated that up to 192 million people were infected with genital HSV-1 and up to 491 million people were infected with HSV-2 in 2016 [24]. Because the clinical treatment demand for genital herpes is higher than that for other herpes, the need to develop a therapeutic vaccine targeting HSV-2 compared to HSV-1 tends to be more emphasized.

After primary infection, HSV remains dormant or latent in the host's ganglia and can be periodically reactivated to cause chronic infection [25]. Since HSV does not show any special clinical symptoms during latent infection, it is possible to develop an HSV therapeutic vaccine that basically target the same antigen as the prophylactic vaccine. To effectively suppress HSV reactivation, many research is underway to discover target antigens that can induce a strong neutralizing immune response. Furthermore, due to the nature of viruses that infect mucous membranes, specific formulations and inoculation routes that can induce mucosal immunity are also considered important factors. Currently, several clinical trials for the development of therapeutic vaccine targeting HSV are underway (Table 5).

Hepatitis B Virus

Hepatitis B virus (HBV) is a virus that causes acute and chronic hepatitis B, and is spread through infected blood or body fluids [26]. It is estimated that more than 2 billion people are infected with HBV worldwide, of whom approximately 250 million are chronically infected with hepatitis B [27].

Chronic HBV infection is defined as HBV persisting for more than 6 months with hepatitis B surface antigen (HBsAg) detected in the blood [26]. In the case of chronic infection with HBV, the immune response (especially T cell response) of the infected person is weakened and dysfunction occurs [28], so complete clearance of the HBV genome in chronic HBV patients is considered impossible. Therefore, the ultimate goal of a therapeutic vaccine for chronic HBV infection is proposed to be "functional treatment" that overcomes the decline in HBV-specific T cell function in chronic carriers. Currently, a therapeutic vaccine for chronic HBV patients developed as a virus-like particle formulation has been approved for use in Cuba [29], and several other vaccine candi-

Table 4. Current status of clinical trials for therapeutic vaccines targeting VZV

Vaccine	Antigen	Formulation	Clinical stage	ID[a]
EG-HZ	gE	Recombinant protein	Phase 1	NCT04210752
CVI-VZV-001	gE	Recombinant protein	IND for Phase 1	-
JCXH-105	gE	mRNA vaccine[b]	Phase 1	NCT05871541
mRNA-1468	gE	mRNA vaccine	Phase 1/2	NCT05701800

VZV, varicella zoster virus; mRNA, messenger RNA.
[a]ClinicalTrials.gov registration number of representative clinical study. [b]Self-amplifying RNA vaccines.

Table 5. Current status of clinical trials for therapeutic vaccines targeting HSV

Vaccine	Antigen	Formulation	Clinical stage	ID[a]
gD-Alum/MPL	HSV-2 gD	Recombinant protein	Phase 3	NCT00057330
HerpV	HSV-2 32-peptides +HSP70	Recombinant protein	Phase 2	NCT01687595
GEN-003	HSV-2 gD2ΔTMR+ICP4.2	Recombinant protein	Phase 2	NCT01667341
HSV529	HSV-2 ΔUL5/ΔUL29 HSV-2	Live attenuated virus	Phase 1	NCT02571166
mRNA-1608	Not disclosed	mRNA vaccine	Phase 1/2	NCT06033261
BNT163	HSV-2 gC, gD, gE	mRNA vaccine	Phase 1	NCT05432583

HSV, herpes simplex virus; mRNA, messenger RNA.
[a]ClinicalTrials.gov registration number of representative clinical study.

 https://doi.org/10.7774/cevr.2024.13.1.21

dates are currently undergoing clinical trials (Table 6).

Mycobacterium Tuberculosis

Tuberculosis (TB) is a representative bacterial chronic infectious disease caused by infection with *Mycobacterium tuberculosis*. It mainly infects the lungs and causes respiratory diseases. In addition, bacterial invasion into other organs can cause meningitis, pleurisy, and peritonitis [30]. In the latent infection state, there are no symptoms, but when the infected patient's immunity weakens, the infected pathogen progresses to active TB [31]. According to the WHO, the number of TB patients worldwide in 2022 was 10.6 million, an increase of 4.5% compared to the previous year (10.1 million). Additionally, the number of deaths due to TB was 1.6 million, a 6.7% increase compared to the previous year (1.5 million) [32].

TB treatment requires fairly long-term antibiotic administration, but the emergence of antibiotic-resistant strains is becoming more frequent, which poses a major obstacle to treating chronic TB. In addition, the BCG (Bacillus Calmette-Guérin) vaccine, the only approved TB vaccine, has been reported to be not very effective in adolescents or adults [33], so there is a great need to develop a new vaccine suitable for treating chronic TB. Accordingly, efforts are continuing to develop new therapeutic vaccines targeting chronic and latent TB infection (Table 7).

Conclusion

Therapeutic vaccine is a relatively recent concept, and so far, there has been a tendency to focus on cancer treatment (therapeutic cancer vaccines) targeting neo-antigen of malignant neoplasms rather than infectious diseases. On the other hand, the research and development trends of therapeutic vaccines targeting infectious diseases are still relatively insufficient compared to prophylactic vaccines. Numerous prophylactic vaccines have already been approved for use, and many clinical trials of vaccine candidates are in progress. However, there are still no vaccines for the treatment of chronic infectious diseases, only except for the shingles vaccines, and the number of development studies that have entered clinical trials is very limited.

There are several factors contributing to the relative lack of development of therapeutic vaccines for chronic infectious diseases. First of all, in the case of chronic infectious diseases, the clinical manifestations of chronic infectious diseases vary depending on the characteristics of the pathogens, and as a result, the main targets of therapeutic vaccines also show very different aspects depending on the subject. Because vac-

Table 6. Current status of clinical trials for therapeutic vaccines targeting HBV

Vaccine	Antigen	Formulation	Clinical stage	ID[a]
NASVAC	HBsAg, HBcAg	Virus like particle	Phase 3 (approved for use in Cuba)	NCT01374308
CVI-HBV-002	L-HBsAg	Recombinant protein	Phase 2	NCT04289987
GS-2829 & GS-6779	HBsAg	Viral vectored vaccine	Phase 1	NCT05770895
TherVacB	HBsAg, HBcAg	Viral vectored vaccine	Phase 1	NCT05727267

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBcAg, hepatitis B core antigen.
[a]ClinicalTrials.gov registration number of representative clinical study.

Table 7. Current status of clinical trials for therapeutic vaccines targeting tuberculosis

Vaccine	Antigen	Formulation	Clinical stage	ID[a]
MV	*Mycobacterium vaccae*	Inactivated virus	Phase 3	NCT01977768
RUTI	Detoxified *M. tuberculosis* fragment	Detoxified split vaccine	Phase 2	NCT01136161
MIP	*M. indicus pranii*	Inactivated virus	Phase 3	NCT002655226
VPM1002	rBCG-expressing LLO and urease deletion	Live attenuated virus	Phase 2/3	NCT03152903
BCG	*M. bovis Bacillus Calmette-Guerin*	Live attenuated virus	Phase 1	NCT01119521
ID93+GLA-SE	RV1913, Rv2608, Rv3619, Rv3620	Recombinant protein	Phase 2	NCT02465216
H56:IC31	Ag85b, ESAT6, Rv2660c	Recombinant protein	Phase 2	NCT03512249
MVA85A	Rv3804c, mycolyl transferase	Viral vectored vaccine	Phase 1	NCT00456183
AERAS-402	Ag85A, Ag85b, TB10.4	Viral vectored vaccine	Phase 2	NCT02414828

rBCG, recombinant Bacille Calmette-Guerin; LLO, listeriolysin O.
[a]ClinicalTrials.gov registration number of representative clinical study.

cines with different therapeutic targets inevitably require different approaches to factors such as development strategy, vaccine efficacy evaluation technology, and clinical approval standards, therapeutic vaccines should be grouped according to the target symptoms and mechanism of action of the vaccine. Therefore, it is necessary to conduct research on vaccine development and evaluation methods appropriate for the characteristics of each chronic infection. The groups of therapeutic vaccines proposed in this study are as follows: (1) vaccine for symptomatic treatment, (2) vaccine to prevent recurrence, and (3) vaccine for remission (elimination) of infectious agents.

The absence of standardized immunogenicity analysis techniques for therapeutic vaccines is another factor that needs to be addressed. Appropriate treatment of a disease that has transitioned into a chronic infection requires a method that can directly kill the infected cells. Since cellular immunity plays a major role for this, in is necessary to standardize the evaluation method for T cell immune response in order to develop a therapeutic vaccine. However, unlike humoral immunity, the measurement of cellular immunity requires experimentally complex processes and equipment, and because the activity of cellular immunity shows very large variations for each individual/period/tissue, there are still no clear standard protocols and procedures.

Nevertheless, it has been confirmed that global efforts are being made to develop therapeutic vaccines based on various formulations for representative chronic infectious diseases with high clinical demand. In particular, due to the recent success of messenger RNA (mRNA) vaccines in coronavirus disease 2019 pandemic, new possibilities for vaccine development against various infectious diseases that have long been considered incurable are being presented, and development efforts are being attempted by applying mRNA formulations to therapeutic vaccines. Research on therapeutic vaccines based on the mRNA platform is currently undergoing clinical trials for most of the chronic infectious diseases investigated in this study, and it is expected that this novel platform can play a positive role in the development of therapeutic vaccines in the future.

In order to develop a successful therapeutic vaccine, along with the progression of vaccine formulation technology and immunotherapy technology, standardization of test methods and the establishment of evaluation standards to verify the efficacy of vaccine substances are additional elements that must be established. To achieve this, research on the pathological characteristics of each chronic infectious disease and an accurate understanding of the immunological factors necessary for defense/treatment of each chronic infection are prerequisite. It also includes efforts to discover latent infection and reactivation-specific antigens, develop cell-mediated immunogenicity measurement technology, and establish standard/reference materials. If these current issues are shared at the national level with academia and industry, and research capabilities are focused and supported in necessary areas, it is expected that effective responses to chronic infectious diseases through therapeutic vaccines will be possible in the future.

ORCID

Pil-Gu Park *https://orcid.org/0000-0002-3024-3439*
Munazza Fatima *https://orcid.org/0000-0002-1212-9667*
Timothy An *https://orcid.org/0000-0002-4356-6827*
Ye-Eun Moon *https://orcid.org/0009-0004-5808-1664*
Seungkyun Woo *https://orcid.org/0009-0003-3574-8406*
Hyewon Youn *https://orcid.org/0000-0003-1006-2689*
Kee-Jong Hong *https://orcid.org/0000-0003-2054-7014*

References

1. Farmer PE. Shattuck Lecture. Chronic infectious disease and the future of health care delivery. N Engl J Med 2013; 369:2424-36.
2. Mancuso G, Midiri A, De Gaetano S, Ponzo E, Biondo C. Tackling drug-resistant tuberculosis: new challenges from the old pathogen Mycobacterium tuberculosis. Microorganisms 2023;11:2277.
3. Temereanca A, Ruta S. Strategies to overcome HIV drug resistance-current and future perspectives. Front Microbiol 2023;14:1133407.
4. de la Fuente-Nunez C, Cesaro A, Hancock RE. Antibiotic failure: beyond antimicrobial resistance. Drug Resist Updat 2023;71:101012.
5. Boukhebza H, Bellon N, Limacher JM, Inchauspe G. Therapeutic vaccination to treat chronic infectious diseases: current clinical developments using MVA-based vaccines. Hum Vaccin Immunother 2012;8:1746-57.
6. McCance DJ. Human papilloma viruses. Amsterdam: Elsevier; 2002.
7. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, coun-

try and HPV type. Int J Cancer 2017;141:664-70.
8. Kash N, Lee MA, Kollipara R, Downing C, Guidry J, Tyring SK. Safety and efficacy data on vaccines and immunization to human papillomavirus. J Clin Med 2015;4:614-33.
9. Furumoto H, Irahara M. Human papilloma virus (HPV) and cervical cancer. J Med Invest 2002;49:124-33.
10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. IARC Monogr Eval Carcinog Risks Hum 2012;100(Pt B):1-441.
11. Khan G, Fitzmaurice C, Naghavi M, Ahmed LA. Global and regional incidence, mortality and disability-adjusted life-years for Epstein-Barr virus-attributable malignancies, 1990-2017. BMJ Open 2020;10:e037505.
12. Chang MS, Kim WH. Epstein-Barr virus in human malignancy: a special reference to Epstein-Barr virus associated gastric carcinoma. Cancer Res Treat 2005;37:257-67.
13. Forte E, Zhang Z, Thorp EB, Hummel M. Cytomegalovirus latency and reactivation: an intricate interplay with the host immune response. Front Cell Infect Microbiol 2020;10:130.
14. Ison MG. Diagnosis of gastrointestinal cytomegalovirus infections: an imperfect science. Clin Infect Dis 2013;57:1560-1.
15. Nichols WG, Boeckh M. Recent advances in the therapy and prevention of CMV infections. J Clin Virol 2000;16:25-40.
16. Gershon AA, Breuer J, Cohen JI, et al. Varicella zoster virus infection. Nat Rev Dis Primers 2015;1:15016.
17. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med 1995;155:1605-9.
18. Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982;61:310-6.
19. Heininger U, Seward JF. Varicella. Lancet 2006;368:1365-76.
20. Johnson RW, Rice AS. Clinical practice: postherpetic neuralgia. N Engl J Med 2014;371:1526-33.
21. Levin MJ, Weinberg A. Immune responses to zoster vaccines. Hum Vaccin Immunother 2019;15:772-7.
22. Looker KJ, Magaret AS, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. PLoS One 2015;10:e0140765.
23. Looker KJ, Magaret AS, Turner KM, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One 2015;10:e114989.
24. James C, Harfouche M, Welton NJ, et al. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. Bull World Health Organ 2020;98:315-29.
25. Suzich JB, Cliffe AR. Strength in diversity: understanding the pathways to herpes simplex virus reactivation. Virology 2018;522:81-91.
26. Kwon SY, Lee CH. Epidemiology and prevention of hepatitis B virus infection. Korean J Hepatol 2011;17:87-95.
27. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-55.
28. Bertoletti A, Ferrari C. Adaptive immunity in HBV infection. J Hepatol 2016;64:S71-83.
29. Fleites YA, Aguiar J, Cinza Z, et al. HeberNasvac, a therapeutic vaccine for chronic hepatitis B, stimulates local and systemic markers of innate immunity: potential use in SARS-CoV-2 postexposure prophylaxis. Euroasian J Hepatogastroenterol 2021;11:59-70.
30. Carabali-Isajar ML, Rodriguez-Bejarano OH, Amado T, et al. Clinical manifestations and immune response to tuberculosis. World J Microbiol Biotechnol 2023;39:206.
31. Lee SH. Tuberculosis infection and latent tuberculosis. Tuberc Respir Dis (Seoul) 2016;79:201-6.
32. Bagcchi S. WHO's global tuberculosis report 2022. Lancet Microbe 2023;4:e20.
33. Hatherill M, Cobelens F. Infant BCG vaccination is beneficial, but not sufficient. Lancet Glob Health 2022;10:e1220-1.