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Review Article

Advances in NCD Vaccines: At Glance -

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ABSTRACT

Nearly 71% of all deaths occur due to Non-Communicable Diseases (NCDs) worldwide. Over 85% of the total premature deaths occur in low- and middle- income countries. Cardiovascular diseases are the most killer ones among NCDs (17.9 million) followed by cancers (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million). There must be availability of effective, affordable and broadly accessible medicines for their treatment. As per exigency of the time, it is relevant enough for researchers, especially now days, to focus more upon preventing NCDs. In this sequence, the researchers have been working actively to bring out NCD vaccines successfully for last decade and had therefore published many research papers. This research study aimed at disseminating their essence at a glance thus, to enrich the literature.

The biological basis for these vaccines is T lymphocytes; more especially Cytotoxic T cells that have a co-receptor called CD8 (cluster of differentiation 8) on their cell surfaces. CD8 is a transmembrane glycoprotein that serves as a co-receptor. Cytotoxic CD8 T cells carry out their killing function by releasing two types of preformed cytotoxic proteins: the first granzymes that seems able to induce apoptosis in any type of target cell, and the second pore-forming protein (i.e. perforin), that punches holes in the target-cell membrane through which the granzymes can enter. The natural killer cells, activated in response to interferons or macrophage derived cytokines, serve to trap viral infections whereas the adaptive immune response that produces antigen specific cytotoxic T cells, clear the infection. The Natural Killer (NK) T cells; relatively more larger, are a subset of T cells that express TCR αβ chains as well as a variety of NK cell markers. These cells recognize both exogenous and endogenous lipid antigens in the context of the Major Histo-Compatibility (MHC) like molecule CD1d. Human T cells express MHC class II antigens and adhesion molecules characteristic of Antigen Presenting Cells (APCs) as were evident in vitro as well as in vivo. The main function of Major Histocompatibility Complex (MHC) class II molecules is to present processed antigens. The MHC class II molecules are derived primarily from exogenous sources to CD4+ T lymphocytes that are critical for the initiation of the antigen-specific immune response. CD8+ T cells play important roles in clearing viral infections and eradicating tumors. The Natural Killer cells work to control viral infections by secreting IFNγ and TNFα. A low or inverted CD4/ CD8 ratio is an immune risk phenotype and is associated with altered immune function, immune senescence, and chronic inflammation in both HIV infected and uninfected populations. The prevalence of an inverted CD4/ CD8 ratio increases with age. CD8+ T cell immunity could be boosted by the intravenous infusion of autologous EBV specific cytotoxic CD8+ T cells after expansion in vitro or by the administration of agents such as interleukin 7, which expands the population of functional virus specific CD8+ T cells in chronic viral infection.

Our immune system is highly dependent on the nutrients in our blood stream, and our blood stream is made mostly of water! If we don't have enough water, we can properly not transport nutrients to each organ system and then to its each cell. Further, milk containing probiotics, calcium, vitamin D and immunoglobulins, and trace amount of other vitamins boost our immune system. Foods rich in vitamin C include oranges, grapefruits, tangerines, strawberries, bell peppers, spinach, kale and broccoli also boost our immune system in addition to consumption of enough selenium, adequate zinc supplementation, vitamin A, E, Folic acid, Proteins and Iron. Proper rest and sleep are conditions to have a good immune system functioning.

Designing vaccines that elicit effective CD8+ T cell responses requires a thorough knowledge of the pathways of antigen presentation in vivo. The recent progress in understanding the activation of naïve CD8+ T cells in vivo, with a particular emphasis on cross-priming, has illustrated the presentation mechanism of protein antigens acquired by dendritic cells from their environment. Thus, with the rapid advances in this area of research, the dawn of rational vaccine design is at hand. A search of the literature was undertaken in various online journals especially emphasis on those that were freely accessible for their published literature using a combination of NCD, NCD Vaccines and health system related keywords and subject headings. The selected articles were independently appraised using a tool based on critical appraisal checklists developed by the Critical Appraisal Skills Programme (CASP) UK. This article is a descriptive analysis of the published and grey literature on health system responses to NCDs and NCD Vaccines. The vaccines that treat a cancer patient are named as treatment or therapeutic vaccines. There are varied treatment vaccines available that have different ways of their working. They destroy all cancer cells to keep the cancer away from recurring. They remain activated in the immune system even after the treatments and seize a metastasizing cancer**.** Two kinds of cancer preventing vaccines had been approved almost more than a decade ago by the Food and Drug Administration (FDA) of the United State of America. The one i.e. Sipuleucel-T and another is IMLYGIC. As the name suggests that HPV vaccines protect against the Human Papillomavirus (HPV), is already available in market though research. However, it still continues on the research to develop more effective vaccines that succor treatment of each stage of various types of the cancer in cervix. Another approved vaccine that is nasally administered safeguards human beings against the Hepatitis B Virus (HBV). There are other NCD vaccines which are under trial include bladder cancer vaccine, brain tumor vaccine, breast cancer vaccine, colorectal cancer vaccine, kidney cancer vaccine, lung cancer like mesothelioma, myeloma cancer vaccines, pancreatic cancer vaccine and prostate cancer vaccine. Development of NCD vaccines had not only addressed cancer and hypertension but also addiction, obesity, asthma, arthritis, psoriasis, multiple sclerosis, and Crohn's disease. Similar to the traditional vaccines, targeting rather than pathogens or pathogen infected cells, NCD vaccines work by modulating the human immune system targeting cells, proteins or other molecules that are associated with the NCD in line. The article explains how NCD vaccines differ from traditional vaccines, and describes some regulatory implications of this innovative type of therapeutics. Traditional vaccines can prevent the disease in a healthy person arising from certain cancers causing viruses. Moreover, there are numerous benefits for these traditional vaccines as discussed in the discussion part of this study. Although these characteristics and considerations contrast sharply with those of NCD vaccines, raising the question of whether the term vaccine is appropriate for this new category of drugs, NCD vaccines have their potential, need more research and development to get effectively adopted by public during the forthcoming time

Keywords: Basis for NCD Vaccines; CD8 + T cell immunity; IFNγ; TNFα; Interleukin 7

INTRODUCTION

NCD global burden

According to WHO (2018), globally an equivalent to 71% of all deaths occur due to Non-Communicable Diseases (NCDs) that is equal to 41 million people each year; 15 million between the ages of 30 and 69 years; over 85% of these premature deaths occur in low- and middle-income countries [1]. Cardiovascular diseases are most killers among NCDs and 17.9 million people suffer from cancers (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million). Approximately 10 million people have been diagnosed with cardiovascular and respirator cancer, currently, over 22 million people are cancer patients globally [2] and more than 6 million people use to loss their lives due to the disease annually [2].

A new estimates on the global cancer burden indicated that it had risen to 19.3 million cases and 10 million cancer deaths in 2020 [3]. The global burden of hypertension in 2010 was approximately 1.4 billion i.e. 31.1% of adults people [4], more than 1.0 billion hypertensive adults were living in low and middle-income countries (28.5%, 349 million people) where mean BP control rates were 7.7% and likely to exceed the projected 1.6 billion by 2025 [4].

Atherosclerosis annually accounts for at least 30% of all deaths all over the world thus represents a grave health problem. It significantly reduces life expectancy by 8-12 years in the 60 year old patients because of a poor prognosis depending on the vascular event [5]. Diabetes prevalence was estimated to be 9.3% (463 million people) globally in 2019, might rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [6]. It was higher in urban (10.8%) than rural (7.2%) areas. It was higher (10.4%) in high-income than low income countries (4.0%) [6].

There is an urgent need for therapies that can prevent the shifting burden of non-communicable diseases. A need that is nowadays being met with increased efforts to develop NCD vaccines. Moreover, it is always desirable that people should achieve an increased life expectancy. Since 1900 the global average for the life expectancy has more increased to be double now over the past 70 years [7]. However, the inequality in the life expectancy is still very high across and within countries. Central African Republic with 53 years record (2019) was having the lowest life expectancy while it was 30 years longer in Japan [7].

Rationale of the study

As per exigency of the time, now days, it is relevant enough for researchers to focus more on preventing NCDs since their global burden is very high. There must be availability of effective, affordable and broadly accessible medicines for their treatment. Therapeutic B-cell vaccines aim at inducing neutralizing autoreactive antibodies against important disease mediators [8]. Therefore, numerous animal models have demonstrated that active immunotherapy can induce disease modifying levels of autoantibodies. Similarly, the researchers have been working to trial out NCD vaccines successfully and actively for last decade. They had published many research papers. This research study aimed at disseminating their essence at a glance thus, to enrich the literature.

MATERIAL: BIOLOGICAL BASIS FOR NCD VACCINES

Unlike most organs, the thymus is a special organ. It continues to grow after the birth reaching the relative maximum size by puberty [8] thus, it is the most active in fetal and neonatal life and it is the largest in children [8]. It increases to 20-50 grams by puberty [8]. Once puberty is reached, the thymus starts to shrink slowly by way of the thymic involution hence the size decreases and gets replaced by fat [8]. The thymus possesses a remarkable capacity to regenerate itself after even an injury. The thymus remains hardly a little not more than a fatty tissue by the age of 75 [8].

Fortunately, the thymus by puberty forms all the needed T cells in an individual [9]. After the T and B lymphocytes have matured respectively in the thymus and bone marrow, they then travel to the lymph nodes (located throughout the body) and spleen where they remain and work until the immune system is activated [9]. T cells or T lymphocytes are type of leukocytes (white blood cells) that are an essential part of the immune system. T cells are one of the two primary types of lymphocytes whereas B cells are the second type that determines the specificity of immune response to antigens or foreign substances in the body. There are 3 main types of T cells: cytotoxic, helper, and regulatory [9]. Each of them has a different role in the immune response. Cytotoxic T cells (Tc cells) have a co-receptor called CD8 on their cell surfaces. The CD-8 (Cluster of Differentiation - 8) is a transmembrane glycoprotein that functions as a co-receptor for the T Cell Receptor (TCR) [10]. Natural Killer cells are relatively larger granular lymphocytes than the Natural Killer T cells. The Natural Killer (NK) T cells are a subset of T cells that express TCR, α and β chains as well as a variety of NK cell markers [10]. These cells recognize both exogenous and endogenous lipid antigens in the context of the Major Histo-Compatibility (MHC) like molecule CD1d [11]. Human T cells express major MHC class II antigens and adhesion molecules that are characteristic of Antigen-Presenting Cells (APCs) as were evident *in vitro* as well as *in vivo* [11]. The main function of Major Histocompatibility Complex (MHC) class II molecules is a critical one for provoking the antigen-specific immune response that occurs due to presentation of processed antigens. These are derived primarily from exogenous sources, to CD4+ T lymphocytes [12].

CD8+ T cells play important roles in clearing viral infections and eradicating tumors [13]. Designing vaccines that elicit effective CD8+ T cell responses requires a thorough knowledge of the pathways of antigen presentation in vivo. The recent progress in understanding the activation of naïve CD8+ T cells in vivo, with a particular emphasis on cross-priming, has illustrated the presentation mechanism of protein antigens acquired by dendritic cells from their environment [13]. Thus, with the rapid advances in this area of research, the dawn of rational vaccine design is at hand.

All NCDs have a common feature to develop in humans i.e. immune system weakening. There are so many risk factors which weaken the immune system if the exposure to the risk factors is not eliminated. The weakness manifest as certain signs & symptoms include as follows:

(1) Stress Level is Sky High

(2) Always Have a Cold

(3) Have Lots of Tummy Troubles

(4) Wounds are Slow to Heal

(5) Have Frequent Infections

(6) Feeling of Tiredness all the Time

Tests used to diagnose an immune disorder manifested as the weakened immune system can determine normal levels of infection-fighting proteins (immunoglobulin) in blood and measure the levels of blood cells and immune system cells [14]. Abnormal numbers of certain cells can indicate an immunological defect [14]. A normal ratio of CD4/ CD8 is greater than 1.0, with CD4 lymphocytes ranging from 500 to 1200/ mm3 while CD8 lymphocytes from 150 to 1000/ mm3 [14]. If the ratio is higher than 1, it means immune system is strong and person may not have HIV. If the ratio is less than 1, means that person may have HIV. A low or inverted CD4/ CD8 ratio is an immune risk phenotype and is associated with altered immune function, immune senescence, and chronic inflammation in both HIV infected and uninfected populations [14]. The prevalence of an inverted CD4/ CD8 ratio increases with age [14]. A person's viral load is considered durably undetectable when all viral load test results are undetectable for at least six months after their first undetectable test result [14]. This means that most people will need to be treated for 7 to 12 months to have a durably undetectable viral load [14].

CD8+ T cell immunity could be boosted by the intravenous infusion of autologous EBV specific cytotoxic CD8+ T cells after expansion in vitro or by administration of agents such as interleukin 7, which expands the population of functional virus specific CD8+ T cells in chronic viral infection [15]. During this process, the CD4+ helper T cells license the dendritic cells to give a potent activating signal to the naive CD8+ T cells [15] of CD8+ T cells mediated by CD40 signaling [14,15]. Once the naïve CD8+ T cell is bound to the infected cell, it is triggered to release CD40 [14,15]. When the perfectly shaped virus antigen on an infected cell fits into the Killer T-cell receptor, the T cell releases perforin and cytotoxins [15]. Cytotoxins go directly inside the cell through their pores, destroying it and any viruses inside [15]. This is why Killer T cells are also called Cytotoxic T cells. Cytotoxic CD8 T cells carry out their killing function by releasing two types of preformed cytotoxic proteins: the granzymes, which seem able to induce apoptosis in any type of target cell, and the pore-forming protein perforin, which punches holes in the target-cell membrane through which the granzymes can enter [16]. The Natural Killer cells are activated in response to interferons or macrophage derived cytokines. They serve to contain viral infections while the adaptive immune response produces antigen specific cytotoxic T cells that can clear the infection. The Natural Killer cells work to control viral infections by secreting IFNγ and TNFα [17].

Medications may be prescribed to increase T cell count. No specific foods have been shown to increase the number of WBCs or T cells in the body. However, a healthy diet can help to boost the immune system overall. Our immune system is highly dependent on the nutrients in our blood stream, and our blood stream, in turn, is made mostly of water! If we don't have enough water, we can properly not transport nutrients to each organ system and then to its each cell. We need to increase hydration when we are fighting infections, so we'll need to double down on water [18]. Further, similarly, Milk contains nutrients like probiotics, vitamin D and immunoglobulins that boost the immune system and in turn reduce the risk of allergies [19]. While we mostly relate milk with bone-strengthening calcium, it can help reduce cardiovascular diseases and chances of one getting a stroke. Vitamin A supports the thymus and stimulates the immune response [19]. Daily supplementation with high dose of vitamin C maintains the size and the weight of the thymus and increases the number of T cells. In fact, Vitamin C is one of the biggest immune system boosters. A lack of vitamin C can even make anyone more prone to getting sick quickly. Oranges, grapefruits, tangerines, strawberries, bell peppers, spinach, kale and broccoli are rich in vitamin C [20]. We also need enough selenium for immunity against viruses and cancer [21]. Not enough protein in our diet can weaken our immune system. Our body also produces proteins when we sleep that help our body fight infection. For this reason, lack of sleep reduces our immune defenses. Cancers and chemotherapy drugs can also reduce immunity [22]. An adequate Zinc supplementation results in increased numbers of T and NK cells and elevated production of IL (Inter Leukine) 2 and sIL 2R. Furthermore, lymphocytic response to phytohemagglutinin stimulation as well as to NK cell activity improved significantly compared to the placebo group when the impact of Zinc supplementation was researched out [23]. The same T cells that benefit from sleep give rise a part of the body's response to viruses and bacteria [24], and one of the key ingredients that primes those T cells for action is vitamin D [25]. So we should take daily sun bath for a reasonable time in the morning. Moreover, to maintain an adequate level of vitamin A & E, Folic acid and Iron is necessary. Vitamin E can be a powerful antioxidant that helps our body fight off infection [26]. We can incorporate garlic in our diet. It has many immune booting properties. Moreover, there are certain healthy ways which strengthen our immune system like (1) take steps to avoid infection, such as washing hands frequently, (2) never do smoking, (3) exercise regularly and have proper rest, (4) maintain a healthy weight, (5) eat a diet that stands for high in fruits and vegetables, (6) if drink alcohol, drink only in moderation, (7) if drink tea or coffee, drink herbal tea or any of the following teas: *Turmeric, Ginger, Licorice Root, Peppermint, Chamomile, Lemongrass, Hibiscus or Black Tea*, (8) consume fermented foods, (9) drink bone broth, (10) consume foods those are high in protein such as lean meats and poultry, and (11) foods (the great sources of zinc are oysters, nuts, fortified cereal, and beans) that are high in zinc (stock up) – the Zinc a mineral that increases the production of white blood cells and T cells, which fight infection, and (12) get adequate sleep [24,26], Firstly, the antibodies neutralise the virus, meaning that it is no longer capable of infecting the host cell. Secondly, many antibodies can work together, causing virus particles to stick together in a process called agglutination. In addition, infection-fighting antibodies and cells are reduced during periods when one doesn't get enough sleep [24,26]. So, our body needs sleep to fight infectious diseases. Long-term lack of sleep also increases a risk of obesity, diabetes, and heart and blood vessel (cardiovascular) disease [24-26].

The phytonutrients in honey are responsible for its antioxidant properties, as well as its antibacterial and antifungal power [27]. They're also thought to be the reason raw honey has shown immune-boosting and anticancer benefits. Heavy processing destroys these valuable nutrients [27]. Further, as a super source of (vitamin B 6, bananas can also aid our immune system [28], help form red blood cells, ensure a well-functioning nervous system, and assist protein metabolism [28]. So we should enjoy a banana each day, at breakfast on our whole grain-cereal or before our workout at the gym [28].

However, chronic Non Communicable Diseases (NCDs) such as cancer, hypertension, atherosclerosis, and diabetes are increasingly recognized as the major cause of morbidity and mortality worldwide. Vaccines are one of the greatest achievements in the field of modern medicine, dramatically reducing the incidence of serious or life threatening infectious diseases and allowing people to live healthier and longer. Likewise, we need to discover efficient NCD vaccine to get rid of these diseases.

METHODOLOGY

Internet search and study of all the relevant research papers and their findings (literature search and review) with more focus on latest research studies (i.e. last 6 years) was made using different search combinations like Non Communicable Diseases (NCD), immunologic assays, NCD vaccines and other health system inter-related keywords and subject headings in various online journals with an especial emphasis on those that were freely accessible for their published literature [29].

NCD references compiled at the WHO Western Pacific Regional Office were also searched for the pertinent data. Moreover, eligible references and reviews deemed as meeting inclusion criteria [29,30] were also taken in to the account for the present study. Search terms used for the review were NCD Vaccines, non-communicable-diseases-vaccines, noncommunicable diseases, chronic illness, chronic diseases, cancer, cardiovascular diseases, heart diseases, stroke, diabetes mellitus, atherosclerosis, chronic respiratory diseases, lung diseases, obstructive or occupational lung diseases, pulmonary disease, chronic obstructive or lung disease, asthma, silicosis, diet, exercise, and middle-income country, low income countries, developing countries, health system performance, health system bottlenecks, health system strengthening, health reform, organization and administration, responsiveness, efficiency, quality, service delivery, health care provision, health services, health care service, health service delivery, service delivery, access, accessibility, coverage, health promotion, patient safety, patient education, patient information, patient compliance, inclusion and exclusion criteria. Only published relevant literature to NCDs and NCD Vaccines in English from January 2015 to December 2020 with full text (accessible) articles was assessed. In accordance with the NCD health systems interventions, research and developmental activities especially on the NCD Vaccines and other efforts and their different outcomes were taken in to the account: measures of incidence, prevalence, morbidity or mortality, sensitivity, specificity, efficacy &/ efficiency, changes in quality of care, health service providers, coverage of services, etc.

The study design [31] included no limit in the review of the qualified literature recognizing many NCD vaccines trials, overall scenario of non-communicable diseases and a bit of the potential interventions. However, the implementation research often lacks experimental studies. No study that provided only opinions with lack of evidence based research method(s) was included for the analysis [31].

Nonetheless, the research articles focused on non-communicable diseases or chronic diseases were also included in the review on the assumption that findings may still be relevant [31].

Data mining and quality information on basic characteristics for the appraisal (study design, study setting, non-communicable diseases, NCD vaccines of focus) and outputs of each article were included to extract down information into a standardized data tool and cross-checked for any inconsistencies [32].

A tool based on critical appraisal checklists [33] developed by the Critical Appraisal Skills Programme (CASP) UK was employed to do independent appraisal of all the selected articles. Opinion differences with peers review were resolved through discussion to provide an indication of the quality of studies exploring NCDs and NCD Vaccines.

This article is a descriptive analysis [34] of the published and grey literature to bring about advance information on NCD Vaccines; moreover, as indicated that the quality of publications were reviewed as randomized controlled trials, non-controlled trials, or descriptive studies to give some indication of the rigor used to produce the research findings [34].

AVAILABLE NCD VACCINES

The vaccines that meant for immunotherapy or treatment of existing cancer are called treatment vaccines. They boost the immune system of the body to fight against the existing cancer [35]. These vaccines have varied mode of action. They destroy all cancer cells to keep the cancer away from recurring. They remain activated in the immune system even after the treatments and take hol of a cancerous tumor from spreading or growing again [35]. The cancer cells with their surface antigens or epitopes are the substances that are detrimental thus immune system, in most cases, bouts on the antigens in order to get rid of their harmful impacts. This phenomenon equips immune system with memory development to combat the antigens sooner or later [35].

Vaccines for cancers

A clinical trial for the ISA101 vaccine, developed by ISA Pharmaceuticals, based in Leiden, Netherlands, has also been made to test and treat an advanced cervical cancer positive for HPV 16, a strain of the virus responsible for more than half of cervical cancers [41]. A study published in the Science Translational Medicine on March 18, 2020, had found that 31 of 72 patients treated with the vaccine along with chemotherapy had tumor shrinkage [41]. Further, the patients with the stronger immune response to the vaccine lived longer than those with the weaker response [41].

While a preventive HPV vaccine triggered production of antibodies to block the virus from infecting cells, a therapeutic HPV vaccine had induced T cells to eradicate cells that had been infected [42]. The ISA101 vaccine was given as an injection to the patient that delivered certain peptides; the small parts of the virus particles found inside HPV had infected the cancer cells [44].

"People with advanced cervical cancer generally have compromised immune systems, which helps explain why therapeutic vaccines on their own have been ineffective", says the study's senior author Sjoerd H. van der Burg, a cancer immunotherapy researcher at Leiden University Medical Center" [44]. He and his colleagues decided to combine ISA101 with chemotherapy after they found that the chemotherapy typically used to treat cervical cancer killed some cells. "These cells dampen the immune response to cancer. "Interestingly, the chemotherapy doesn't destroy the T cells that are needed to increase the immune response to the vaccine," van der Burg says [44].

Another trial, published in the January 2019 issue of JAMA Oncology, showed that combining ISA101 with an immune checkpoint inhibitor could improve response to the vaccine. Larger randomized trials would test whether ISA101 used alongside a checkpoint inhibitor, chemotherapy or both were superior to standard care [44].

Hepatitis B virus vaccine (NASVAC)

This approved nasally administered vaccine can cause liver cancer though it protects human beings from the infection of Hepatitis B

Virus (HBV) [45]. This virus can cause liver cancer [45]. NASVAC is an experimental therapeutic vaccine that targets two different Hepatitis B Virus (HBV) antigens, led to a reduction in hepatitis B surface antigen levels and several study participants achieved a functional cure after 18 months of follow-up, according to report at the AASLD virtual Liver Meeting [45]. Unlike the widely used vaccines for hepatitis B prevention, NASVAC aims at treating people who already had chronic HBV infection [45]. The vaccine contained both Hepatitis B Surface Antigen (HBsAg) and Core Antigen (HBcAg) [45]. The combination triggered the production of anti-HBs antibodies and promoted T-cell activity against the virus [45]. Osamu Yoshida of Ehime University Graduate School of Medicine in Japan presented updated results from a study of 71 people who had received ten doses of NASVAC and were followed for up to 18 months [45]. The study included 29 symptomatic participants taking nucleoside/ nucleotide antiviral drugs and 42 asymptomatic untreated people; out of both the groups, 22 and 33 respectively, had reached the 18-month mark [45]. Antivirals such as tenofovir disoproxil fumarate (Viread), tenofovir alafenamide (Vemlidy) and entecavir (Baraclude) could suppress HBV replication indefinitely during treatment, but they seldom led to a cure [45]. The treatment was normally harmless, thriving and tolerated nicely, without any severe hostile events. Yoshida reported last year that ALT (Alanine Transferase) levels remained stable in the antiviral group but some people in the untreated group experienced steep increases [45]. One of them went on experiencing HBeAg loss after an ALT flare. Yoshida said, "HBsAg levels continued to decline with longer follow-up after receiving NASVAC [45]. Anti-HBs antibody levels rose after vaccine administration, but then gradually decreased during extended follow-up period [45]. A total of six people achieved a functional cure, including two who did so during the extended follow-up period hence the Nasal administration of NASVAC could be an effective and safe immune therapy for achieving functional cure in chronic hepatitis B patients" [45].

NCD vaccines under trial

Whatsoever vaccines developed for the communicable diseases as well as non-communicable diseases had their roots in clinical trials for their successfulness. These are the key for researchers who are engaged in testing vaccines for many types of cancer.

Vaccine for bladder cancer

Researchers are trying to test out how a sound vaccine can be made from a virus altered with the HER 2 antigen, the surface antigens or molecules found on bladder cancer cells [46]. The immune system acquires memory to find and destroy these tumor cells when these are exposed to the virus [46]. There is a dilemma among researchers that if the standard bladder cancer treatment works better or the standard bladder treatment with a vaccine works better? Another, the Bacillus Calmette Guerin (BCG) vaccine when it is injected into the body, it uses a weaken bacteria to activate the immune system of the body to treat early stage of the cancer in the bladder [47].

Vaccine for brain tumor

There are many researchers who are attempting to test treatment vaccines for brain tumor. They aimed at focusing on certain molecules (epitopes) [48] on the surface of brain tumor cells. Some focus on newly found brain cancer cells whereas others focus on recurring ones. Majority of such studies are being conducted on children and teens.

Vaccine for breast cancer

Many research studies are going on testing the treatment or therapeutic vaccines given alone or given with other treatment options available for breast cancer. The researchers are conducting their clinical trials or working to develop vaccines that can prevent breast cancer even at any stage.

Vaccine for colorectal cancer

The treatment vaccines that let the body's immune system to attack on cells that contain colorectal cancer antigens like Carcinoembryonic Antigen (CEA), MUC 1, Guanylyl Cyclase C, and NY ESO 1 are being attempted to be developed by many researchers globally [49].

Kidney cancer vaccine

Many kidney cancer treatment vaccines are being tested by many researchers globally even to prevent kidney cancer in its later stages from coming back. Most types of kidney cancer do not react nicely to traditional chemotherapy, thus, research for kidney cancer emphases more on newer and different treatment options to be available, for example, as immunotherapy and targeted therapy [50].

Recently, many discovered medicines that affect angiogenesis or cancer cell growth are being tested as targeted therapies for kidney cancer [50]. Apart from these, many other immunotherapies as adjuvant therapies are also available to treat kidney cancer quickly. The adjuvant therapies are treatments which are given after the main treatment to lower down the risk of recurrence and to get rid of any remaining cancer cells. For example, sunitinib as a targeted therapy slowed the cancer from recurrence after a nephrectomy [50].

Leukemia vaccine

Studies on treatment vaccines for various types of leukemia, such as Acute Myeloid Leukemia (AML) and Chronic Lymphocytic Leukemia (CLL) help other available treatments for them, such as a bone marrow or stem cell transplantation. The vaccines that developed from a person's cancer cells and other cells might help the immune system destroy the cancer cells [51].

Vaccines for lung cancer

Melanoma: Many vaccines for treatment of melanoma, given alone or with other treatments, are under research. The vaccines contain antigens to destroy melanoma cells that let the immune system to destroy other melanoma cells inside the body [52].

Myeloma: The treatment vaccines developed for the multiple myelomas are under clinical trials. These vaccines are near the re-mission to arrive to the market soon. Researches are also being made to test vaccines for smoldering myelomas need autologous bone marrow/ stem cell transplant [53].

Pancreatic cancer vaccine: Many treatment vaccines for pancreatic cancer have already been designed to boost the immune system's response and thereby to combat pancreatic cancer cells. These vaccines might be given as the only treatment or along with another treatment [54]. These vaccines will arrive to the market soon.

Prostate cancer vaccine: The Sipuleucel T (Provenge) vaccine for metastatic or spreading prostate cancer had been approved by the FDA of USA in 2010. The Sipuleucel T is tailored to each person through a series of steps like firstly white blood cells are removed from the person's blood and then altered in a laboratory to target

prostate cancer cells. These altered cells are, in turn, injected back into the person *via* veins [55]. This happens similarly as to a blood transfusion. These modified cells impart the immune system to discover and finish prostate cancer cells. The recent studies are trying to know if it helps people for their earlier stage cancers [55].

This new vaccine, known as CYT006AngQb, works by inhibiting angiotensin II, a molecule that constricts blood vessels and raises blood pressure. Several existing medications target the same molecule, including ACE (angiotensin converting enzyme) inhibitors and ARBs (angiotensin receptor blockers) [56].

It has recently been reported that an angiotensin II (AngII) vaccine for hypertension successfully attenuated elevated blood pressures in an animal model without any immunogenic side effects. In this system, an immunogenic molecule (i.e., KLH) with adjuvants provided an antigen that had supported the activation of helper T cells [56]. In addition, pretreatment with the AngII vaccine exerted neuroprotective effects in a cerebral ischemia model and cardioprotective effects in a myocardial infarction model. In the early phase of clinical trial, the administration of an AngII vaccine (AngQb-Cyt006) successfully decreased blood pressure in hypertensive patients with the increase of anti-AngII antibody titer [56]. Increasing the effectiveness of drug adherence interventions in the clinical setting might have a large impact on the health of the population, which could be improved by using successful therapeutic vaccines [56].

The vaccine needs further testing, especially to see if the body would be allowed any escape mechanism that would allow it to raise blood pressure if and when needed. Based on current observations from preclinical studies, the premise for vaccination to reduce atherosclerosis is based on the existence of immune responses against LDL or apo B 100 related peptide antigens in vivo and ability of immunization with these antigens to modulate such responses by affecting cellular immune [56].

DISCUSSION

Development of NCD vaccines not only addressed cancer and hypertension but also addiction, obesity, asthma, arthritis, psoriasis, multiple sclerosis, and Crohn's disease. Similar to the traditional vaccines, targeting rather than pathogens or pathogen infected cells, NCD vaccines work by modulating the human immune system targeting cells, proteins or other molecules that are associated with the NCD in line. Despite their name, NCD vaccines differ in significant ways from the traditional infectious disease vaccines like infectious disease vaccines are often administered to healthy people, generally children, therefore, the tolerability and willingness. The efficacy of infectious disease vaccines is generally high, and the vaccines disburse benefits to the population level associated with herd immunity and potential eradication of the diseases in question. Moreover, the task of approving new treatments like NCD vaccines on the basis of their efficacy and safety seems an interesting and challenging enough to various authorities. There are certain underlined questions like, should NCD vaccines be evaluated under the same analytic frame work as traditional vaccines, or that of biologic drugs do?

Nonetheless, cancer treatment vaccines are the immune system's ability booster to catch and finish the cancer causing antigens. The cancer cells often contain certain molecules or cancer specific antigens on their exterior while the healthy cells do not contain that. When these surface molecules or antigens are injected to a person as a vaccine, they let the immune system to catch and finish cancer cells in the body. Some cancer vaccines are personalized and produced from the person's tumor samples (biopsy) that are removed during surgery while other cancer vaccines are not personalized that target non-specific antigens. Most cancer treatment vaccines are only offered through clinical trials, which are research studies that use patients as volunteers.

Therapeutic cancer vaccines aim at specifically activating antitumor CTL already present in the blood or the tumor of the cancer patients. They appear safer and better controlled, firstly because vaccination focuses specifically on the activation of anti-vaccine T cells and secondly because the T cells targeted by the vaccine undergo thymic selection, a process that should minimize the occurrence of undesirable immune responses against self-antigens expressed by normal tissues. More specifically, antigenic peptides identified from mixed-tumor lymphocytes cultures in vitro by the stimulation with autologous tumor cells of T cells originating from cancer patients, should be the safest, as they generally target antigens against which a previous spontaneous response has been mounted, usually without any noticeable side effects. On the other hand, the safety of antigens identified using the reverse immunology approach, that is, the in vitro priming of healthy donor or cancer patient T cells with pulsed dendritic cells should be appropriately evaluated, as it is not always known whether these antigens can be safely targeted by the immune system.

No adverse events were observed in the cohorts of patients who were previously vaccinated using peptide, full-length protein or virus containing MAGE-1 or MAGE-3, even in the few responding patients. Interestingly, following vaccination, patients who responded to the vaccine were shown to display a considerable enrichment of antitumor T cells in their metastases, when compared to anti-vaccine T cells, suggesting that activation of only a few anti-vaccine CTL can lead to the priming or reactivation of T cells recognizing tumor antigens unrelated to the vaccine.

The cancer begins and grows in the first place by suppressing the immune system. An adjuvant, a substance added to a vaccine, are used to fix the problem of immune suppression as well as by improving the body's immune response. Cancer cells rise from healthy cells of a person's own organ system. Resultant, the cancer cells may not appear as harmful to the immune system hence, the immune system generally ignore the cells besides catching and rebelling them.

Why a cancer vaccine along with other treatment is given to treat a cancer? The first most reason is that larger or more advanced tumors are too hard to treat with the treatment vaccine alone. Recent findings from clinical trials have indicated that self-reactive antibodies can also be readily induced in humans; therapeutic efficacy, however, has not always been achieved. To date, clinical experience with vaccines against self-molecules is limited. Choice of the right target, proper vaccine design, optimal vaccine dose and regimen remain the major challenges to achieve clinical efficacy and safety for this novel class of bio therapeutics

Current developments based on the use of T cell stimulating antibodies or on the adoptive transfer of antitumor T cells have highlighted the power of cancer immunotherapy strategies. A significant proportion of the patients treated using these therapies showed remarkable clinical responses and some of these patients even

appeared disease-free several years after initiation of the treatment. Nevertheless, as discussed above, both therapies often lead to the development of strong autoimmune side effects that need to be controlled. Additionally, although the response to adoptive transfer and stimulating antibodies therapies showed great promises, a large number of patients still remain refractory to these treatments.

Generally older people, chronically sick, HIV/ AIDS and cancer patients have weak immune systems, therefore, their bodies after they receiving a treatment vaccine may not be able to produce a strong immune response that limits how well a vaccine works. Also, chemotherapy and radiotherapy may weaken a person's immune system that limit how well the immune system of the body can react to a vaccine. Therefore, some researchers hold opinion that cancer treatment vaccines can work better for smaller tumors or early stage cancers.

Implementation of the Federal National Childhood Vaccine Injury Compensation Act had a basis that looked into the merits and demerits of NCD vaccines like combined substantial benefits at population level, low willingness to pay and low tolerance for adverse events which encourages production and uptakes by providing immunity from liability to industry and compensation to injured patients.

CONCLUSION

The article explores the emerging class of NCD vaccines. The principles and the molecular mechanisms which explain the basis for development of NCD vaccine were stated. Different types, their developmental stages and mode of actions of various NCD vaccines were also explained and discussed. Moreover, it explains how NCD vaccines differ from the traditional vaccines, and also describes challenges and difficulties being faced by the researchers in this field of the novel class of vaccines development. Another, some regulatory implications of this innovative type of therapeutics have also been discussed. Since NCD vaccines are meant for an active treatment of NCDs while traditionally developed vaccines for preventing communicable diseases, need prior injection to the exposure of the disease although these treatment characteristics and considerations of the NCDs contrast sharply with those of conventional vaccines, raising the question of whether the term vaccine is appropriate for this new category of drugs,. There are numerous benefits of the NCD vaccines over the traditional vaccines as already discussed in this study. The NCD vaccines have their own potential; need more research and development as well as devising effective regulatory strategies to get adopted by public during the forthcoming time easily.

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