IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 8 Issue 4, April 2021
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

Current state of affairs for West Nile Virus: Review

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Abstract

West Nile Virus (WNV) is an infectious disease that is usually asymptomatic in about 80% of cases but causes West Nile Fever in 20% of infected individuals. Neurological complications occur in approximately 1% of infected cases leading to severe disease. WNV is mainly transmitted between mosquitoes and birds, however, human and horse infections have been reported although they do not develop sufficient viremia to support transmission by mosquitoes. The purpose of this review was to report the current state of WNV infections and treatment options in humans as published in the literature. Publications on the epidemiology of West Nile Virus, current treatment options and vaccine development were reviewed. Studies have shown that both T cells and antibody immune responses against WNV envelope protein can control replication of WNV. Currently there is no effective treatment or licensed vaccine for West Nile Virus in humans.

Key words: West Nile Virus, vaccines, Immunity

1. Introduction

West Nile Virus (WNV) is a re-emerging single-stranded positive-polarity RNA virus, and a member of the family Flaviviridae (Calisher et al., 1989; Ciota et al., 2008). The RNA genome of WNV is about 11kb long and comprises of three genes that encode structural proteins, and seven genes that encode non-structural proteins. The structural proteins of WNV include the capsid (core), pre-membrane and envelope. On the other hand, the non-structural (NS) proteins comprise the NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 (Chambers, Hahn, Galler, & Rice, 1990). There are also flavivirus family members close to WNV that include the Japanese encephalitis virus (JEV), Saint Louis (SLE) encephalitis virus, Tick-borne encephalitis virus (TBE), Yellow fever virus (YFV), Murray Valley encephalitis (MVE) and Dengue virus (DEV) (Lanciotti et al., 1999). West Nile Virus was first identified in the West Nile District of Uganda in 1937 (Gould & Fikrig, 2004). It infects mainly birds, but humans and horses are also susceptible (Ledizet et al., 2005).

In humans, studies have shown that WNV infection causes West Nile Fever (WNF) disease that may be asymptomatic or cause severe neurological complications. Approximately 80% of infected humans usually remain asymptomatic, 20% may develop febrile illness while less than 1% may develop severe illness including neurologic complications such as meningitis and acute flaccid paralysis (Hayes, Sejvar, et al., 2005). It has been shown that elderly and immunocompromised individuals are most susceptible to WNV infection (Granwehr et al., 2004). Outbreaks of WNV fever and encephalitis diseases have been reported in humans throughout the world since 1990s, including in the Middle East, Europe, Africa (Chepkorir et al., 2019; Dauphin, Zientara, Zeller, & Murgue, 2004), Asia and Australia (Mackenzie, Gubler, & Petersen, 2004). In 1999, the first human cases of WNV infections were reported in the United States (Lanciotti et al., 1999). The infections later disseminated into Mexico, South America, Canada and the Caribbean (Deardorff et al., 2006; Komar & Clark, 2006). The major challenge is lack of effective prevention or treatment for WNV disease in humans. This warrants great efforts to develop preventive vaccines.

2. Transmission and Epidemiology

The WNV infection is mainly transmitted between mosquitoes and birds. Human and horse infections do not develop sufficient viral loads for transmission and therefore are considered as dead end hosts (Hayes, Komar, et al., 2005). Transmission of the virus across continents has been attributed to infected migratory birds (Rossi, Ross, & Evans, 2010). Infected mosquitoes carry WNV in their salivary glands, which they transmit to susceptible bird species (e.g. crows), humans or horses during a blood meal. When infected, birds may die within one week or develop immunity that may last their entire life. A sufficient level of viremia is required in birds for mosquitoes to obtain enough virus quantity to be transmitted from the infected birds to the next hosts. In the case of humans, WNV transmission has been reported to be mainly through mosquito bites, but also less commonly through blood transfusion (Charatan, 2002), organ transplantation (Charatan, 2002), intrauterine (Alpert, Fergerson, & Noel, 2003) and through breast feeding (Hayes, Komar, et al., 2005). The distribution of WNV is global and includes Europe, Asia, Africa, Australia (Kunjin virus) and North, Central and South America (Mackenzie et al., 2004). Currently, there is no human vaccine against WNV. Historically, finding an effective vaccine against WNV would be the most effective method of protection against human WNV infections.

3. Disease symptoms of West Nile Virus infections

Studies have shown that WNV disease is usually more severe in the elderly people because of immune senescence and children due to immature immune system (Petersen & Roehrig, 2001). West Nile Virus infections predominantly cause West Nile fever (WNF) in infected individuals across all age groups, but could be higher in younger individuals (Hayes, Sejvar, et al., 2005). Mild disease has been shown to manifest as headaches, feeling of fatigue and muscle pains, and occasionally causing nausea and vomiting (Watson et al., 2004). WNF may also lead to death as

a result of cardiologic and pulmonary complications (Sejvar, Lindsey, & Campbell, 2011). Severe WNV disease has been shown to cause meningitis and encephalitis that is associated with damage to the central nervous system in humans (Omalu, Shakir, Wang, Lipkin, & Wiley, 2003). Meningitis due to WNV may also cause severe headache, fatigue and muscle pains similar to mild disease (Sejvar et al., 2003). WNV encephalitis leads to state of confusion in affected individuals that may progress to neurologic disease, coma and death, especially in the elderly and immunocompromised individuals (Ravindra et al., 2004). Severe disease may also lead to severe neurological syndromes such as tremor of the upper extremities, Parkinsonism, postural instability and gait disturbance leading to falls (Burton et al., 2004). Other complications associated with WNV infections include WNV poliomyelitis that may lead to limb weakness or paralysis (Sejvar et al., 2005) and long-term neurologic sequelae after survival from such neurological complications.

4. Immune responses to West Nile Virus infections

Studies in animal models indicate that both innate and adaptive immune responses play vital roles to protect against primary infection by virulent strains of WNV (Samuel & Diamond, 2006).

4.1 Innate Immunity to West Nile Virus: After viral infection, the innate immune system is activated to secrete cytokines, mainly anti-viral type I IFN-α and IFN-β (Samuel & Diamond, 2006). In vitro studies have that these interferon inhibit the replication of WNV (Anderson & Rahal, 2002) and control the replication and dissemination of the virus (Samuel & Diamond, 2005). The cytoplasmic pattern recognition receptors, regulator of interferon gene (RIG)-I and interferon regulatory factor (IRF)-3 have been shown to mediate the IFN inducing pathway stimulated by WNV infection in the immune cells (Fredericksen, Smith, Katze, Shi, & Gale, 2004). There is therefore, some evidence to show that the innate immune system plays an important role in the fight against WNV infections.

4.2 Adaptive T cell immune responses to West Nile Virus: Type II IFN-γ secreted by viral activated T cells has been associated with in vivo anti-viral activities against WNV infections. Studies have shown that IFN-γ was required for prevention of the spread of WNV and associated death in mice infected with WNV, and γδ T cells were important in IFN-γ generation (Wang et al., 2003). CD4+ and CD8+ T cells that produce Type I (α/β) and type II ( ) interferons shown to participate in the clearance of WNV from peripheral tissues and the central nervous system in mice infected with WNV (Samuel & Diamond, 2006; Shrestha, Ng, Chu, Noll, & Diamond, 2008). The CD4+ T cells could also contribute to protection against WNV disease by promoting antibody production through released cytokines that prime B cells. In addition, CD4+ T cells may provide help that sustains WNV-specific CD8+ T cells through cytokine production. CD4+ T cells with cytotoxic function have also been shown to protect mice against WNV dissemination to the central nervous system in WNV-infected mice (Brien, Uhrlaub, & Nikolich-Zugich, 2008; Sitati & Diamond, 2006). Additional studies that used adoptive transfer of α/β T

cells into mice that were later infected with WNV reported a reduction in WNV infection in the mice (Brien, Uhrlaub, & Nikolich-Zugich, 2007; Wang et al., 2003) demonstrating the role of α/β T cells in the generation of anti-viral immunity. Further studies to demonstrate the role of CD8+ T cells in protection against WNV disease showed that genetic deficiency of CD8+ T cells in mice caused a reduction in the survival rates of mice after challenge with WNV (Shrestha et al., 2008). The role of CD8+ T cells was again demonstrated by adoptive transfer of WNV-specific CD8+ T cells that were shown to protect recipient mice against WNV challenge (Brien et al., 2007). In conclusion, studies have shown that CD4+, CD8+ and α/β T play a role in adaptive immunity against WNV using mouse model.

4.3 Antibody immune responses to West Nile Virus: In addition to T cell activity against WNV, WNV-specific antibody responses have been shown to play a critical role in the control against viral replication and clearance of viremia through IgM (Shrestha et al., 2008; Ulbert, 2019). Studies have demonstrated that B-cell deficient mice are more susceptible to WNV infection, leading to high viral titers in the central nervous system. This observation suggested that antibodies produced by B cells are required curbing viral replication. The role of humoral immunity against WNV infection was also shown by passively transferred anti-WNV immune serum that provided protection to recipient mice against lethal challenge with WNV (Diamond, Shrestha, Marri, Mahan, & Engle, 2003; Engle & Diamond, 2003). More so, transfer studies of human gamma globulin from human donors that were previously exposed to WNV provided protection to recipient B cell deficient mice (Engle & Diamond, 2003), attributing the protection to the transferred antibodies. Studies using passive immunization of hamsters with immune serum from hamsters infected with WNV NY385-99 provided protection against challenge with WNV, indicating that antibodies play a vital role in protection (Tesh et al., 2002). Therefore, putting together, studies have shown that both antibody and T cell adaptive immune responses may work in synergy to provide effective protection against WNV infection and reduce disease severity.

5. Status of West Nile Virus Treatment

Currently there is no known cure for WNV infections in humans. Patients with severe complications due to WNV disease mainly receive supportive care (to reduce pain, maintain hydration and promote rest) (Sejvar, 2014). In vitro studies have demonstrated that interferon-α inhibits WNV-induced cell death. However, in vivo studies have not been conducted fully to ascertain the benefits of interferon-α in protection against WNV disease (Morrey et al., 2004). Other therapeutic studies have been performed in animal models using WNV specific immune globulin from human donors who had previous exposure to WNV infections. Use of such antibodies provided protection in an advanced case of human neurological disease diagnosed with WNV infection (Walid & Mahmoud, 2009). Similar studies in mice have demonstrated protection against WNV disease when administered with WNV-specific immunoglobulins before onset of WNV disease (Beigel et al., 2010; Engle & Diamond, 2003; Smeraski, Siddharthan, &

Morrey, 2011). Based on the literature review above, it is clear that effective treatment against WNV should target involvement of both antibody and T cell activities.

6. West Nile Virus Vaccine development

In regard to anti-WNV vaccine development, several candidate vaccines have been developed since the disease was identified. The following are some of the development milestones reported:

6.1 DNA vaccines: DNA vaccines for WNV have been shown to elicit protective immunity in animal models. Plasmid DNA, that encode pre-membrane and envelope proteins, have been shown to prevent horse, crows and mice from WNV viremia and mortality (Davis et al., 2001). The DNA-based vaccines induced serum WNV neutralizing antibodies in horses that were protective against infected mosquito challenge (Davis et al., 2001). Similarly, crows that received intramuscular DNA vaccine developed WNV neutralizing antibodies and were protected against challenge with WNV (Turell et al., 2003). Human studies using a DNA vaccine have also been contacted and demonstrated induction of WNV virus neutralizing antibodies in all vaccinated individuals in a phase I clinical trial (Martin et al., 2007). This study also demonstrated induction of WNV-envelope protein-specific CD4+ T cell responses that secreted IFN-γ, but with less CD8+ T cell responses.

6.2 Inactivated WNV viral particles and subunit vaccines: Studies were conduced in hamsters using a Fort Dodge killed WNV vaccine that was given intramuscularly and induced virus hemmaglutination antibodies, and also protected hamsters against challenge with WNV NY385-99 (Tesh et al., 2002). Use of viral particles was also contacted in mice where subcutaneous immunization of mice with purified inactivated WNV NY99 demonstrated induction of WNV virion neutralizing antibodies with higher avidity for the virion proteins (Zlatkovic, Stiasny, & Heinz, 2011). On the contrary, subunit vaccines induce weaker immune responses. A subunit vaccine, recombinant domain III of West Nile Virus envelope protein (EDIII) has been tested in multiple studies with mouse models. Use of EDIII alone or soluble envelope proteins demonstrated induction of weaker antibody responses in mice (Zlatkovic et al., 2011). However, when WNV EDIII was combined with DNA oligonucleotide (CpG) adjuvant it induced serum WNV neutralizing antibodies (Martina et al., 2008). Mice that were immunized with adjuvanted EDIII were also protected against challenge with WNV (Martina et al., 2008). These studies showed that whole viral partical antigens are highly immunogenic and may not require use of adjuvants while subunit vaccines may require incorporation of vaccine adjuvants in order to induce stronger immunity. Recent studies with HydroVax-001 WNV (a hydrogen peroxide inactivated whole virion) vaccine that was combined with aluminum hydroxide as adjuvant demonstrated induction of virus neutralization antibodies in 50% of intramuscularly immunized human subjects in a phase I clinical trial (Woods et al., 2019).

6.3 Live attenuated Chimerivax-WNV vaccines: Recent studies have developed ChimeriVax-WNV, a live attenuated vaccine produced by the insertion of the genes encoding the pre-

membrane (prM) and envelope (E) proteins of WNV NY99 into the yellow fever (YF) 17D vaccine clone. ChimeriVax-WNV vaccine was administered to hamsters intramuscularly, and induced high in vitro virus neutralizing antibody and hemmaglutination inhibition titers. In addition, vaccinated hamsters were protected against challenge with WNV NY385-99 (Tesh et al., 2002). Human studies with ChimeriVax-WNV have been evaluated in phase II clinical trials and demonstrated high immunogenicity in younger adults and the elderly (Biedenbender, Bevilacqua, Gregg, Watson, & Dayan, 2011; Dayan, Bevilacqua, Coleman, Buldo, & Risi, 2012). The adverse events reported included erythema, swelling, severe headache, severe malaise and severe myalgia that were not significantly higher compared to placebo groups (Dayan et al., 2012). This study reported more than 90% seroconversion in vaccinated individuals and a higher titer of virus neutralization antibodies. Induction of WNV neutralizing antibodies has been shown by many studies as a better correlate of vaccine protection against WNV infection. Since no vaccine has been licensed for human use, additional work is required to search for a safer and effective vaccine against WNV in humans.

7. Challenges of studies with West Nile Virus using mice model

Most preclinical research studies on WNV vaccines and WNV disease pathogenesis have been performed in mice (Samuel & Diamond, 2006). While the mice provide a readily available animal model for research on WNV disease, there are a number of important issues that must be considered with the use of mice in studies of WNV infectious challenge. Most studies have documented incomplete mortality with WNV infection in naïve mice as controls. For example, Qiao M et al reported 20% mortality (Qiao et al., 2004), while Liu and others reported 60% mortality after infection of BALB/c mice with WNV NY99 (Liu et al., 2006). The lack of complete or near total mortality after WNV challenge in non-immunized mice greatly confounds determining the protective benefit of candidate WNV vaccines, especially if the vaccine does not provide total protection. However, the incomplete mortality observed after WNV challenge in mice represents a mouse model with morbidity and mortality characteristics similar to WNV infection of humans since only a small portion of WNV-infected humans have neurological complications or death (Sejvar, 2014).

8. Conclusion

In conclusion, more studies are required to develop an effective vaccine against WNV in humans in order to be prepared for any re-emergency of this episodic disease. Vaccination has been shown over the years as the most effective form of prevention against infectious disease. The use of WNV envelope protein has been shown to generate antibodies that inhibit virus replication.

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