West Nile virus disease therapeutics

Review of the literature for healthcare providers

Overview

No antiviral or adjunctive therapies are approved or recommended for the treatment of West Nile virus (WNV) disease; clinical management is supportive. There are numerous case reports and case series regarding the use of various products (e.g., standard and hyperimmune polyclonal immune globulin, monoclonal immune globulin, interferon, ribavirin, and corticosteroids) in patients with WNV disease. Several of these products have been studied in controlled clinical trials for infections due to WNV or closely related flaviruses (i.e., St. Louis encephalitis and Japanese encephalitis viruses). None have shown benefit. However, the studies often had small sample sizes and the results from some of the clinical trials have not been published. Since polyclonal immune globulin and interferon alpha-n3 are available, some physicians have chosen to use them to treat transplant recipients and other severely immunocompromised patients but there is no proven benefit.

Recent narrative review articles have summarized the scientific basis, preclinical studies, and clinical experience with potential therapeutic agents (Diamond 2009; Beasley 2011). There are no ongoing clinical trials or products available for compassionate use. Updated information about ongoing or completed clinical trials is available at http://clinicaltrials.gov/ct2/results?term=west+nile+virus&Search=Search.

Polyclonal immunoglobulin intravenous (IGIV)

1. [Winston 2014] A case series reports use of polyclonal IGIV to treat four patients (aged 51–63 years) with WNV disease transmitted through organ transplantation in the United States in 2011. All received 500 mg/kg per day IGIV but for variable numbers of days beginning 15–20 days post-transplant. In addition to IGIV, two patients received interferon-alpha2b, one patient received interferon-α2b and WNV IgG-positive plasma, and one patient received ribavirin. Two patients died and two survived; one of the survivors received a second liver transplant at 27 days after the first procedure. In the authors review of the literature of transplant recipients with donor-derived WNV infection, three (43%) of seven patients with encephalitis treated with IGIV alone or IGIV with WNV-IgG containing plasma improved, and all four patients with asymptomatic WNV infection treated with IGIV or plasma survived. However, five (71%) of seven transplant recipients with encephalitis and receiving only supportive care also improved.

2. [Rhee 2011] A case report documents use of polyclonal IGIV to treat a 51-year-old male with WNV encephalitis who was infected through a liver transplant in 2009. The patient received two doses of IGIV (400 mg/kg) administered 4 days and 8 days after onset of symptoms. The patient survived with no known sequelae.

3. [Li 2003] A case series reports the use of polyclonal IGIV (1,000 mg/kg/day for 2 days) to treat two of five patients with WNV acute flaccid paralysis in Michigan in 2002. Timing of the treatments was not described. No significant improvement was observed.

4. [Saquib 2008] A case report documents use of polyclonal IGIV to treat a 32-year-old male kidney transplant recipient with WNV encephalitis in 2005. The patient was infected by mosquito bite approximately 2 months after receiving the transplant. He received 1,000 mg/kg at 2 days after admission and a second dose of 500 mg/kg the following day. The patient recovered with no known sequelae.

5. [Planitzer 2009] The proportion and levels of WNV neutralizing antibody titers in U.S. plasma-derived IGIV increased significantly from 2003–2008. In 2008, approximately 40% of U.S. derived IGIV lots had what might be considered protective levels of antibodies. However, plasma obtained from people with confirmed WNV infection had neutralizing antibody titers 100-fold higher than that found in the IGIV.

Polyclonal IGIV with high titers of WNV antibodies derived from Israeli blood donors (Omr-IgG-am)

1. [Hart 2014] A clinical trial performed in the United States from 2003–2006 randomized 64 patients with WNV encephalitis or acute flaccid paralysis to receive Omr-IgG-am, polyclonal IGIV, or placebo. Only limited results have been published but they showed no differences in outcomes between the study groups. Omr-IgG-am is no longer available in the United States (NCT00068055 http://www.clinicaltrials.gov/ct2/show/study/NCT00068055?term=west+nile+virus&rank=6).

2. [Makhoul 2009] A case series reports use of Omr-IgG-am to treat eight patients (aged 44–63 years) with WNV disease in Israel in 2007. Five patients had encephalitis, one had acute flaccid paralysis, and one had non-neuroinvasive disease. All received 5 days of therapy (400 mg/kg/day). Six patients recovered and two died. The authors noted that earlier therapy seemed to be associated with better response.

3. [Morelli 2010] A case report documents use of plasma obtained from WNV-seropositive blood donors and Omr-IgG-am to treat a 25-year-old female who was viremic with WNV after being infected through a liver transplant in 2009. The organ recipient was asymptomatic but viremia was detected 3 days after transplant; the recipient was tested after the organ donor tested positive on routine screening performed after the transplant. The patient received 10 days of plasma infusions (300–600 mL/day) and another 10 days of Omr-IgG-am (400 mg/kg). The patient survived with no known sequelae.

4. [Levi 2010] A case report documents use of Omr-IgG-am to treat a 57-year-old female lung transplant recipient with WNV encephalitis in 2000. The patient was infected by mosquito bite approximately 2 years after receiving the transplant. She received Omr-IgG-am 13 days after admission but did not survive.

5. [Walid 2009] A case report documents use of Omr-IgG-am to treat a 55-year-old male with WNV acute flaccid paralysis in 2005. The patient had diabetes mellitus and hypothyroidism but no other underlying medical conditions. He was treated with corticosteroids and plasmapheresis from 3–6 days after illness onset. Beginning 8 days after illness onset, he received Omr-IgG-am (400 mg/kg/day) for 7 days. He survived and was transferred to inpatient rehabilitation at 28 days after illness onset.

6. [Haley 2003] A 2003 case report documents use of Omr-IgG-am to treat a 55-year-old male with chronic lymphocytic leukemia and WNV encephalitis. The patient received five doses (500 mg/kg) of Omr-IgG-am starting 6 days after onset of symptoms. The patient died 32 days after onset of illness.

7. [Hamdan 2002] A case report documents use of Omr-IgG-am to treat a 42-year-old male lung transplant recipient with WNV encephalitis in 2000. The patient was infected by mosquito bite approximately 6 months after receiving the transplant. He received one dose of Omr-IgG-am (400 mg/kg) approximately 7 days after onset of symptoms and recovered with no known sequelae.

8. [Shimoni 2001] A case report documents use of Omr-IgG-am to treat a 70-year-old female with chronic lymphocytic leukemia and WNV encephalitis in 2000. The patient received 400 mg/kg approximately 3 days after admission. The patient recovered with no known sequelae.

WNV recombinant humanized monoclonal antibody (MGAWN1)

1. A clinical trial performed in the United States from 2009–2011 randomized 13 patients with WNV disease to receive a single intravenous infusion of MGAWN1 (30 mg/kg) or placebo. Two of six MGAWN1 recipients died compared to 1 of 7 placebo recipients. The study was terminated due to inability to enroll subjects. The results have not been published and the product is no longer available (NCT00927953; http://clinicaltrials.gov/ct2/show/NCT00927953?term=west+nile&rank=1).

2. [Beigel 2010] A phase 1 safety and pharmacokinetics dose-ranging study evaluated MGAWN1 in 40 healthy adults; 30 received one infusion of the study drug and 10 received placebo. Six subjects in the study group experienced 11 drug-related adverse events (diarrhea, chest discomfort, oral herpes, rhinitis, neutropenia, leukopenia, dizziness, headache, and somnolence); one subject was diagnosed with schizophrenia 50 days after receiving the study drug. The highest dose had a half-life of 27 days and exceeded serum target levels by 28-fold.

Interferon

1. [Solomon 2003] A randomized clinical trial performed in Vietnam from 1996–1999 evaluated 117 children with Japanese encephalitis randomized to receive interferon (10 million units/m^2 of body surface area daily for 7 days) or placebo. Japanese encephalitis virus is a flavivirus that is closely related to WNV. Outcome at discharge and 3 months did not differ between the two treatment groups; 20 (33%) of 61 children in the interferon group had a poor outcome (death or severe sequelae), compared with 18 (32%) of 56 in the placebo group (p=0.85, difference 0.1%, 95% CI –17.5 to 17.6%). There were no long-term side effects of interferon.

2. [Rahal 2004] Safety and efficacy of interferon-alpha2b was evaluated in open-label study of 15 patients with St. Louis encephalitis virus neuroinvasive disease during an outbreak in Louisiana in 2001. St. Louis encephalitis virus is a flavivirus that is closely related to WNV. Patients received an initial 3 million units intravenously, followed by 3 million units administered subcutaneously 12 hours later, and then daily for 14 days; treatment was started 1–4 days after hospital admission. Treated patients were compared to 17 untreated patients hospitalized before the study began. Treated patients appeared to have better muscle function and respiratory status in the 1–2 weeks after hospitalization but the study design could not control for initial differences between the groups. Eleven (73%) treated patients developed transient neutropenia or mild hepatitis during therapy.

3. [Wehbeh 2004] An unblinded controlled study in the United States in 2002–2003 randomized 38 patients with WNV neuroinvasive disease to receive interferon-alpha2b (N=19) or supportive care (N=19). However, only 23 patients (15 treated and 8 untreated) were included in the analysis. Neurologic improvement measured by the NIH Stroke Scale during the first 3 weeks of hospitalization was statistically greater among patients treated with interferon compared to those who were not. Side effects (neutropenia and hepatitis) were mild and resolved after treatment stopped.

4. [Kalil 2005] A case series published in 2005 reports use of interferon-alpha in two patients with WNV encephalitis. A 43-year-old male with a previous history of lymphoblastic lymphoma and stem cell transplant received interferon-alpha2b using the regimen described in the previous study for 14 days starting 3 days after illness onset. He had no adverse events and fully recovered over the next 9 months. A 54-year-old female receiving immunosuppressive therapy for rheumatoid arthritis was treated with interferon-alpha beginning 3 days after WNV disease onset. She had neutropenia and myalgia during interferon therapy but recovered from the WNV disease with only mild lower limb weakness.

5. [Chan-Tack 2005] A case report documents use of interferon-alpha2b to treat a 76-year-old male with WNV acute flaccid paralysis in 2003. He received the regimen of 3 million units per days for 14 days beginning 17 days after illness onset. He showed no neurologic improvement and subsequently died.

6. [Lewis 2007] A 2007 case report documents use of interferon-alpha2b to treat an 83-year-old male with WNV encephalitis. He received 3 million units per day for 14 days which was started 2–3 weeks after illness onset. The patient's clinical status was already improving prior to treatment but he showed substantial subsequent improvement and recovered to baseline.

7. [Penn 2006] A 2006 case report documents use of interferon-alpha2b and other therapies in a 57-year-old male with B cell lymphoma and WNV encephalitis. He began interferon (5 million units subcutaneously per day) on hospital day 2, ribavirin (600 mg daily) on hospital day 4, and Omr-IgG-am (400 mg/kg) on day 34. Despite these therapies, he had no sustained improvement and died on hospital day 99.

8. [Sayao 2004] A case series describes seven patients with WNV neuroinvasive disease. Three of the patients received 14 day courses of interferon-alpha2b; all improved but there are no comparative data. One of the treated patients developed delayed acute flaccid paralysis after initial improvement.

9. [Winston 2014] In the case series described above under polyclonal IGIV, one of the four patients who developed WNV disease through organ transplantation received IGIV, interferon-alpha2b, and WNV IgG-positive plasma, and two patients received IGIV and interferon-alpha2b. The patient who received IGIV, interferon, and plasma survived; the other two patients died.

Ribavirin

1. [Kumar 2009] A controlled study in India in 2005–2007 randomized children with Japanese encephalitis to receive ribavirin (10 mg/kg per day for 7 days) or placebo. Japanese encephalitis virus is a flavivirus that is closely related to WNV. There was no difference between the two groups in mortality; 19 (27%) of 70 ribavirin recipients died compared to 21 (25%) of 83 in the control group (OR 1.1; 95% CI 0.5–2.4). There were also no statistically significant differences in secondary outcome measures.

2. [Chowers 2001] Thirty-seven patients in a case series of 233 patients hospitalized with WNV disease in Israel in 2000 received enteral ribavirin as an experimental therapy. Patients who received ribavirin were more likely to die (15/37, 41%) than those who did not (18/196, 9%). However, patients receiving ribavirin may have had more underlying medical conditions or more severe disease, and ribavirin was not an independent risk factor for death on multivariable analysis.

3. [Speigel 2002] A 2002 case report documents use of ribavirin in a 4-year-old male with Hodgkin's lymphoma and WNV encephalitis. He began ribavirin (800 mg per day via nasogastric tube for 14 days) on hospital day 8. A gradual improvement was noted within 2 weeks of therapy initiation, and with intensive supportive care he recovered completely after 4 months.

4. [Winston 2014] In the case series described above under polyclonal IGIV, one of the four patients who developed WNV disease through organ transplantation also received ribavirin. The patient survived after receiving a second liver transplant.

Corticosteroids

1. [Hoke 1992] A double-blinded controlled trial in Thailand in 1984 randomized patients with Japanese encephalitis to receive dexamethasone (0.6 mg/kg intravenous loading dose followed by 0.2 mg/kg every 6 hours for 5 days) or placebo. Japanese encephalitis virus is a flavivirus that is closely related to WNV. There was no significant difference between the two groups in mortality at 25 days after admission, days to alert mental status, or normal neurologic status at 3 months after admission.

2. [Pyrgos 2004] A 2004 case report documents use of corticosteroids to treat a 68-year-old previously healthy male with WNV acute flaccid paralysis. He received methylprednisolone 500 mg per day intravenously for 4 days beginning 7 days after admission. The patient survived and gradually recovered upper extremity strength and bowel and bladder function; lower extremities remained weak.

3. [Nakano 2003] A case series from Japan reports the use of methylprednisolone (1,000 mg/day for 3 days) to treat five patients with probable viral encephalitis due to Japanese encephalitis virus (N=2), herpes simplex virus (N=2), and an unknown etiology (N=1) from 1998–2001. All patients also received acyclovir and one received polyclonal IGIV. All patients survived and gradually recovered.

4. [Johnson 1986] In a case series of 15 patients with Japanese encephalitis in Thailand in 1984, six patients received corticosteroids. Of these six patients, two died compared to four of seven who did not receive corticosteroids. The authors did not identify any differences in other clinical or laboratory parameters.

5. [Bakri 2004] Some patients with ocular manifestations of WNV infection have been treated with topical corticosteroids.

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