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 clear benefit. However, the studies often had small sample sizes and the results from some clinical trials have not been published. Since polyclonal immune globulin and interferon alfa are available, some physicians have chosen to use them to treat transplant recipients and other severely immunocompromised patients with WNV disease, but there is no clear proven benefit.

Several review articles have summarized the scientific basis, preclinical studies, and clinical experience with potential therapeutic agents (Diamond 2009; Beasley 2011; Lim 2013). Updated information about ongoing or completed clinical trials is available at: http://clinicaltrials.gov/ct2/results?term=west+nile+virus&Search=Search.

The following sections summarize relevant publications describing use of various products for the treatment of WNV infections or infections with other closely related flaviviruses.

Polyclonal immune globulin intravenous (IGIV)

1. [Hartmann 2017] A case series reports the use of interferon alfa-2b and polyclonal IGIV in two previous organ-transplant recipients (one kidney, and one heart and kidney) with laboratory-confirmed St. Louis encephalitis virus meningoencephalitis in Arizona in 2015. Both organ recipients had their immunosuppression reduced when infectious meningoencephalitis was suspected. One patient received 14 days of interferon alfa-2b (3 million units per day), while the other received 10 days. Both patients also received 5 days of IGIV (0.4g/kg per day). Both patients eventually recovered with no to minimal neurologic sequelae. An additional previous organ-transplant recipient (kidney) with St. Louis encephalitis virus meningoencephalitis died early in their hospital course before receiving any interferon or IGIV.

2. [Rayamajhi 2015] A double-blinded, placebo-controlled trial in Nepal randomized 22 children with suspected Japanese encephalitis virus meningoencephalitis (not confirmed by laboratory testing) to either IGIV containing anti-Japanese encephalitis virus neutralizing antibodies (ImmunoRel, 0.4g/kg per day for 5 days) or placebo. There was no significant difference in death or neurologic outcomes between the two groups.

3. [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 alfa-2b, one patient received interferon alfa-2b 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.

4. [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.

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.

6. [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.

7. [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.

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

Omr-IgG-am is a polyclonal IGIV product from Israel. Based on donor antibody seroprevalence, it is thought to contain high levels of WNV neutralizing antibodies. Omr-IgG-am is no longer available in the United States.

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.

2. [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.

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. [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 may have been associated with better response, though this was a small case series.

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)

MGAWN1 is a high-affinity, humanized monoclonal antibody that targets the E protein of WNV. MGAWN1 is no longer available.

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 (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. There were no reported adverse events in the placebo group. The highest dose of MGAWN1 had a half-life of 27 days and exceeded serum target levels by 28-fold.

Interferon

1. [Hartmann 2017] The case series also described above under polyclonal IGIV reports the use of interferon alfa-2b and polyclonal IGIV in two previous organ-transplant recipients (one kidney, and one heart and kidney) with laboratory-confirmed St. Louis encephalitis virus meningoencephalitis in Arizona in 2015. Both organ recipients had their immunosuppression reduced when infectious meningoencephalitis was suspected. One patient received 14 days of interferon alfa-2b (3 million units per day), while the other received 10 days. Both patients also received 5 days of IGIV (0.4g/kg per day). Both patients eventually recovered with no to minimal neurologic sequelae. An additional previous organ-transplant recipient (kidney) with St. Louis encephalitis virus meningoencephalitis died early in their hospital course before receiving any interferon or IGIV.

2. [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 alfa-2b, and WNV IgG-positive plasma, and two patients received IGIV and interferon alfa-2b. The patient who received IGIV, interferon, and plasma survived; the other two patients died.

3. [Lewis 2007] A 2007 case report documents use of interferon alfa-2b 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.

4. [Penn 2006] A 2006 case report documents use of interferon alfa-2b 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.

5. [Chan-Tack 2005] A case report documents use of interferon alfa-2b to treat a 76-year-old male with WNV acute flaccid paralysis in 2003. He received a 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. [Kalil 2005] A case series published in 2005 reports use of interferon alfa in two patients with WNV encephalitis. A 43-year-old male with a previous history of lymphoblastic lymphoma and stem cell transplant received interferon alfa-2b 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 alfa 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.

7. [Rahal 2004] Safety and efficacy of interferon alfa-2b was evaluated in open-label study of 15 patients with St. Louis encephalitis virus neuroinvasive disease during an outbreak in Louisiana in 2001. 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, 13 of whom were 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.

8. [Sayao 2004] A case series describes seven patients with WNV neuroinvasive disease. Three of the patients received 14 day courses of interferon alfa-2b; all improved but there are no comparative data. One of the treated patients developed delayed acute flaccid paralysis after initial improvement.

9. [Wehbeh 2004] An unblinded controlled study in the United States in 2002–2003 randomized 38 patients with WNV neuroinvasive disease to receive interferon alfa-2b (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.

10. [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. 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.

Ribavirin

1. [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.

2. [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. 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.

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. [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.

Corticosteroids

1. [Chahil 2016] A case report documents the use of high-dose corticosteroids to treat a 21 year-old previously healthy male with WNV-associated brachial plexopathy. The patient received intravenous methylprednisone 1000mg per week for 3 months. There was gradual partial improvement in weakness and the ability to perform activities of daily living.

2. [Alker 2015] A case report documents the use of intravenous methylprednisone to treat a 43 year-old previously healthy female with WNV-associated acute flaccid paralysis of her left lower extremity. The patient received intravenous methylprednisone 125mg BID for several days followed by a steroid taper after hospital discharge. Her left lower extremity weakness and areflexia gradually improved, but there was some residual weakness at 1 year follow-up.

3. [Bakri 2004] In this case review, 4 of 9 patients with ocular manifestations of WNV infection (e.g., choriditis, chorioretinitis, iritis, optic neuritis, vitritistc.) were treated with topical corticosteroids with varying results.

4. [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.

5. [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.

6. [Hoke 1992] A double-blinded controlled trial in Thailand in 1984 randomized 55 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. 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.

7. [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.

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