West Nile Virus Disease Therapeutics

Review of the literature for healthcare providers

Summary

As of July 2023, available data are inconclusive as to the efficacy of various therapeutics and products (e.g., standard and hyperimmune polyclonal immune globulin, monoclonal immune globulin, interferon, ribavirin, and corticosteroids) to treat patients with WNV disease. Larger, prospective, controlled clinical trials are needed to assess efficacy, including factors such as dosing, timing, and patient populations that might benefit from certain treatments.

Background

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 flaviviruses (e.g., St. Louis encephalitis and Japanese encephalitis viruses). None has shown clear benefit. However, the studies often were underpowered to assess efficacy and had other limitations. Since polyclonal immune globulin and interferon alfa are available, some physicians have chosen to use them to treat recipients of solid organ transplants 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). Multiple reports of therapeutic agents assessed in preclinical studies are not included in this review. Updated information about ongoing or completed clinical trials is available at: http://clinicaltrials.gov/ct2/results?term=west+nile+virus&Search=Search.

Data on Specific Products

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. [Lauterio 2023] A case report describes a 69-year-old recipient of a liver transplant who developed WNV encephalitis in Italy one year after transplant. He was treated with IGIV (400 mg/kg/day x 5 days). His immunosuppressive regimen was reduced. He recovered with mild residual neurologic dysfunction.

2. [Abbas 2022] A case series describes eight solid organ transplant recipients (five kidney, one kidney-pancreas, one lung, one liver) with mosquito-borne WNV neuroinvasive disease admitted to one medical center from 2010–2018. Five patients received IGIV (mean total dose 1340 mg/kg). Seven patients had their immunosuppressive regimens reduced. Six patients were alive at a median follow-up of 49.5 months, two had long-term neurologic deficits, and two died from their WNV disease.

3. [Kasule 2022] A case series describes 24 solid organ transplant recipients (nine kidney, five heart, four liver, five kidney-pancreas, and one kidney-heart) with WNV neuroinvasive disease (including 2 donor-derived infections described in Winston et al 2014) admitted to one medical center in Arizona from 2007–2021. Of note, 13 cases occurred during the 2021 WNV outbreak in Maricopa County. Twenty-three patients were treated with either IGIV alone (400-500 mg/kg/day x median of 5 doses [1-7 doses]; one patient received 1000 mg/kg x 1 dose, followed by 400 mg/kg/day) or IGIV in combination with IFN alfa-2b (3 million units/day x median of 7 doses [3-15 doses]; one patient received 5.1 million units/day x 2 doses). Two patients also received WNV antibody-enriched fresh frozen plasma. Twenty-two (92%) patients had their immunosuppressive regimens decreased. The 30-day mortality was 36% (8 patients). Six patients died in hospital from WNV neuroinvasive disease; two patients were transferred to hospice where one died. Six of 14 (43%) patients with acute flaccid paralysis died. Twelve of 16 (75%) discharged patients had residual neurologic sequelae. One patient with relatively mild disease recovered with no specific therapies.

4. [Almajrafi 2021] A case report describes a 38-year-old recipient of a kidney transplant who developed WNV encephalitis in Saudi Arabia one year after transplant. He was treated with IGIV (100 g x 3 days) beginning 19 days post-symptom onset for treatment of motor paresis. The patient improved and was discharged with minimal residual weakness of the lower limbs.

5. [Aziz 2020] A case series describes 11 solid organ transplant recipients (seven kidney, four kidney-pancreas) with mosquito-borne WNV neuroinvasive disease admitted to one medical center from 1994–2018. Two patients received IGIV at 500-1000 mg/kg weekly x 3-4 doses. All patients had their immunosuppressive regimens reduced. No patients died from their WNV disease; two patients had permanent neurologic damage, one patient who was treated with IGIV and one who was not.

6. [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.

7. [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.

8. [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.

9. [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.

10. [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.

11. [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.

12. [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 (OMRIX Biopharmaceuticals, Tel Aviv, Israel) is a polyclonal IGIV product that contains high titers of WNV neutralizing antibodies. Omr-IgG-am is no longer available in the United States.

1. [Gnann 2019; NCT00069316] A phase 1/2 randomized, double-blind, multicenter study conducted in the United States and Canada from 2003–2006 randomized 62 patients with WNV neuroinvasive disease to receive Omr-IgG-am, polyclonal IGIV (with no detectable WNV IgG antibodies), or normal saline. The mean age of patients was 56 years, 66% were male, and one patient was immunocompromised. Patients were given a single dose of study drug with a median time from admission to drug infusion of 2 days; days post illness onset were not provided. The primary endpoint of the trial was medication safety; secondary endpoints were morbidity and mortality. Patients were followed for 90 days after dosing. There were no significant differences found among groups for either safety or efficacy endpoints; however, the study was underpowered to study efficacy outcomes. Other limitations included delays in drug administration, early termination of the study, and use of lower doses of IGIV than recommended for immunomodulatory effects (typically a 5-day regimen of 0.4 g/kg/day). Most study participants were relatively healthy, middle-aged persons, so results may not be generalizable to other populations. This study was critically appraised by [Mbonde 2023].

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. [Unpublished, Accessed July 2023] 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. [Kasule 2022] A case series describes 24 solid organ transplant recipients with WNV neuroinvasive disease treated with IGIV alone or in combination with IFN alfa-2b (see description above under polyclonal IGIV).

2. [Hartmann 2017] A case series reports the use of interferon alfa-2b and polyclonal IGIV in two previous organ transplant recipients (see description above under polyclonal IGIV).

3. [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.

4. [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.

5. [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.

6. [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.

7. [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.

8. [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.

9. [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.

10. [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.

11. [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. [Hodzic 2023] A systematic literature review and meta-analysis was performed to evaluate the use of steroids for treatment of viral encephalitis, including 281 patients with multiple viral etiologies from 50 publications (as of January 31, 2020) and two cohorts of patients from Houston, TX and Linz, Austria (2007–2017). The main outcomes were mortality and number of adverse events. Ten cohorts were included in the meta-analysis (including four studies of Japanese encephalitis virus [Hoke 1992, Johnson 1986, Sarkari 2012, Rathi 1993], one study of St. Louis encephalitis virus (SLEV) [Sauer 1977], the Houston cohort, which included 83 patients (33 WNV and four SLEV disease cases) [unpublished] and the Linz cohort, which included 72 patients (27 TBEV disease cases) [unpublished]. The meta-analysis showed no benefit of steroid therapy on survival; the same was true for all individual subgroups of viruses investigated. The analysis was limited by heterogeneity of studies, small numbers, diverse viral pathogens, varying therapies, incomplete data on clinical outcomes and adverse events, and possible selection and allocation biases.

2. [Colaneri 2023] A multicenter, retrospective, observational study describes 65 patients in Italy who had WNV neuroinvasive disease from 2014–2022. Thirty-three patients (50.7%) received steroids during hospitalization. Six patients were immunocompromised (one in the non-steroid group and 5 in the steroid group [p=0.21]). Steroids included dexamethasone (n=21), methylprednisolone (n=40), and prednisone (n=8). The mean dose in mg of dexamethasone was 13.6 mg/day. Four patients in each group (12%) died during hospitalization. Receiving steroid therapy did not reduce in-hospital mortality or neurologic sequelae at discharge. Immunocompromised status increased the risk of neurologic sequelae at discharge.

3. [Basic-Jukic 2020] A case series describes 13 recipients of kidney transplants who developed central nervous system infections (including two with WNV encephalitis occurring 2 and 7 months after transplant) in Croatia from 2007–2019. One patient with WNV encephalitis received dexamethasone and the other did not receive steroids. Both patients survived but one remained paraplegic (the authors did not report which patient received dexamethasone).

4. [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.

5. [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.

6. [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.

7. [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.

8. [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.

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