Prophylactic and Therapeutic Efficacy of Human Intravenous Immunoglobulin in Treating West Nile Virus Infection in Mice

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West Nile virus (WNV) is a mosquito-borne disease found most commonly in Africa, West Asia, and the Middle East, where up to 40% of the human population possesses antibodies. It is an emerging disease in the United States. Humans infected with WNV develop a febrile illness that can progress to meningitis or encephalitis. In mice, WNV causes central nervous system infection, paralysis, encephalitis, and death. Currently, no specific therapy or vaccine has been approved for human use. We examined the prophylactic and therapeutic efficacy of pooled human plasma (PP) and intravenous immunoglobulin (IVIG) for treatment of WNV-infected mice. Full protection was achieved when the infected mice were treated with pooled plasma or IVIG obtained from healthy Israeli blood donors that contained WNV-specific antibodies. Similar treatments using PP or IVIG obtained from US blood donors had no protective effect. Recovery of the lethally infected mice was dependent on the dose and time of IVIG administration. These results indicate that antibodies play a major role in protection and recovery from WNV infection and that IVIG can be used as first-line therapy.

West Nile virus (WNV), the etiologic agent of West Nile fever, is an emerging mosquito-borne disease in the United States [1]. WNV is a single-stranded plus RNA virus that is taxonomically classified within the Flaviviridae family (genus Flavivirus) and is a member of the serocomplex that includes Japanese encephalitis virus, Saint Louis encephalitis virus, and Murrey Valley encephalitis virus (MVEV) [2]. WNV circulates in natural transmission cycles involving primarily Culex and other mosquito species and birds [3]. Humans are incidental hosts.

WNV was first isolated from a febrile adult woman in the West Nile District of Uganda in 1937 [4]. The virus is endemic in Africa and the Middle East, causing sporadic outbreaks that affect human and domestic animals [5, 6]. It is most commonly found in Africa, West Asia, and the Middle East, where up to 40% of the human population possesses antibodies [7–9]. Most human infections are mild and characterized by a self-limiting acute febrile illness accompanied by headaches, myalgia, polyarthritis, rash, and lymphadenopathy [10–12]. Rarely, acute hepatitis and pancreatitis have been reported. If the virus crosses the blood-brain barrier, it can cause life-threatening encephalitis or meningitis, and WNV was recognized as a cause of severe human meningoencephalitis in elderly patients during outbreaks in Israel (in the 1950s) [10], France (1962), South Africa (1974), India (1980–1981), and Romania (1996) [11, 13].

The renewed interest in WNV stems from the fact that it emerged in the Western Hemisphere for the first time several years ago and, after what was at first a relatively limited spread, has now been found almost all across the United States and in Canada. WNV has also emerged in recent years in temperate regions of...
Europe and Israel, presenting a global threat to public and animal health [13–16]. Since entering North America in 1999, WNV has been found in the Northern United States in mosquitoes, birds, horses, and other animals [17, 18]. In 1999–2000, WNV was responsible for epidemics in Southern Russia and Israel [19–21]. Passive transfer of specific antibodies or immunoglobulins has been shown to abort or modify a number of flavivirus infections, including infection with Japanese encephalitis virus [22, 23] or MVEV [23, 24], Saint Louis encephalitis [23, 25], tickborne encephalitis [26], and 17D yellow fever [27]. It appears, therefore, that the only currently available treatment for viral infection that could provide a state of immediate immunity is passive transfer of specific antibodies [28, 29].

In the present study, we used the murine model of WNV to determine the efficacy of prophylactic and therapeutic intravenous treatments of human immunoglobulin (IVIG) prepared from pooled blood from healthy donors. IVIG is approved for clinical use and has been successfully administered for the treatment of chronic and infectious diseases [30]. The murine model is a good experimental model for such studies, because WNV causes a systemic infection in mice and invades the central nervous system (CNS), resulting in death within 1–2 weeks [31–33]. Our results show that the passive administration of IVIG containing anti-WNV antibodies can prevent or ameliorate the disease process in a time- and dose-dependent manner.

MATERIALS AND METHODS

Mice. Female BALB/c mice were purchased from Harlan Olac at the age of 21 days (body weight, 10–12 g) and used at the age of 4 weeks unless otherwise stated. Outbred ICR (CD1) female mice (Charles River Laboratories) were obtained at the age of 21 days and used at the age of 5 weeks. Age- and sex-matched animals were used as controls. Mice were maintained in isolation cages and kept in our vivarium until used; food and water was available to them ad libitum. The mouse experiments were approved by and performed according to the guidelines of the Ben Gurion University Faculty of Health Sciences Animal Safety Committee.

Cell cultures. A baby hamster kidney (BHK) cell line (BHK-21) [34] was grown in Dulbecco’s modified Eagle medium supplemented with 10% fetal calf serum, 1% nonessential amino acids, 1.2% NaHCO3, and antibiotics. The cells were maintained in a humidified atmosphere at 37°C in 5% CO2 and were used for growing virus stocks and virus titrations.

Virus and virus titrations. The original strain of WNV was isolated in Israel in 1952 from the blood of a human patient during a febrile phase of the disease [10]. After isolation, it was passaged several times in suckling mice brains and Vero cells and then plaque-purified in BHK cells (unpublished data). Signature amino acid motifs show that this strain belongs to lineage I [4, 35]. Virus plaque assays were performed on BHK-21 cells as described elsewhere [36]. Virus titers were expressed as plaque-forming units per milliliter. A single virus stock containing 2 × 106 pfu/mL, prepared on BHK-21 cells and stored in aliquots at −70°C, was used in all studies.

Infection of mice. Four-week-old mice were inoculated intraperitoneally (ip) with 100 pfu (20 LD50) or 1000 pfu (200 LD50) of stock virus. Lethal doses (LD50) were calculated according to the method of Reed and Muench [37].

Virus titration in blood samples and brains from infected mice. Blood samples from the tail vein were obtained from mice 2 and 3 days after infection and collected in serum separator tubes (serum separator; Becton Dickinson). Serum samples were frozen at −70°C until use. Brains were removed from infected mice, rinsed individually in 2 mL of cold PBS containing 2% fetal calf serum, and sonicated, and the suspension was clarified by low-speed centrifugation (1560 g) for 10 min. The supernatants were aliquoted and stored at −70°C until further use. Virus levels in blood and brains were determined by plaque titration on BHK-21 cells.

WNV antigen preparation. WNV antigen was prepared according to the method described by Mahy and Kangro [38], with slight modifications. WNV was grown on BHK-21 cells, and, at the appropriate cytopathic effect (60%–70%), the flasks were frozen overnight at −70°C. After low-speed centrifugation to remove cell debris, the virus was concentrated 20 times by high-speed centrifugation (140,000 g for 90 min) and resuspended in PBS. Virus was inactivated using β-propiolactone (0.001% final concentration). To confirm that virus inactivation was complete, the suspension was tested by plaque assay on BHK-21 cells and in 3-day-old suckling mice. No viral infectivity could be detected by both methods, thus confirming that virus inactivation was complete. This antigen preparation was used at a 1:1000 dilution (in carbonate buffer [pH 9.5]).

Assay of anti-WNV antibodies by ELISA. ELISA was performed according to the method described by Feinstein et al. [39] and Martin et al. [40], with slight modifications. In brief, microtiter plates were coated and incubated overnight at 4°C with 100 µL of a 1:1000 dilution of the antigen. After the incubation, the coating buffer was decanted, and the plates were washed twice in PBS containing 0.05% Tween 20 and 0.2% sodium azide (washing buffer). A blocking step, in which 200 µL/well of PBS with 0.05% Tween 20 and 2.5% nonfat dry milk was used, was added to reduce the overall background and increase the sensitivity of the assay. The plates were then incubated at 37°C for 1 h and washed 4 times in washing buffer, and 100-µL aliquots of mouse serum diluted in dilution buffer (PBS containing 0.05% Tween 20 and 0.5% dry milk) were added to each well (2–4 wells/sample). Negative and positive controls of mouse serum were tested in each plate. The plates...
were incubated for 1 h at 37°C in a humidified atmosphere. After incubation, the plates were washed 5 times, and 100 μL of conjugate anti–mouse IgG (Sigma) was added to each well and incubated at 37°C for 1 h. Then plates were washed 5 times in washing buffer, 50 μL of substrate was added to each well, and plates were incubated at room temperature for 30 min. The color intensity was read by an ELISA microplate reader at an absorbance of 405 nm.

**Virus neutralization assay.** The titer of neutralizing antibodies was determined using a modified plaque-reduction test. In brief, serial 2-fold dilutions (1:5 to 1:320) of IVIG were prepared in 96-well flat-bottom microtiter plates, and 50–100 pfu of WNV was added in an equal volume of solution. The mixtures were incubated for 30 min at room temperature, and then 5 × 10⁴ Vero cells were added to the IVIG-virus mixtures. After 72 h of incubation in a humidified atmosphere at 37°C and 5% CO₂, plaques were counted. Plaque-reduction neutralizing antibody titers are expressed as the reciprocal of the highest dilution that gave 50% plaque reduction.

**Preparation of mouse anti-WNV hyperimmune serum.** Five-week-old ICR mice were injected ip with 50–100 pfu of WNV/mouse. Three weeks later, surviving mice received a booster inoculation of 100 pfu of virus; blood samples were obtained 14 days later. The antibody titer, as measured by ELISA, was 1:3200.

**Immunoglobulin and pooled plasma preparations.** IgG preparations from Israeli donors (IVIG-IL; OMRIGAM 5% intravenous IgG, lots E25191, E44311, and E49341) containing 50 mg/mL IgG (total protein, 5% [wt/vol]) were a gift from Dr. Israel Nur of Omrix Biopharmaceuticals (Ness-Ziona, Israel). Omrix IgG contains all the IgG antibodies that were present in the healthy Israeli adult blood donors (blood was collected at Magen David Adom, Tel-Aviv, Israel, in 1999–2000). This product was found to have an anti-WNV antibody titer of 1:1600 by ELISA and of >1:80 by plaque-reduction test. A preparation of IVIG from US blood donors (IVIG-US; blood was collected at a collection center in Grand River, Youngstown, OH, in 1999; lot E 15132) was found to have a titer of 1:10 by ELISA. Pooled plasma from Israeli donors (PP-IL) and pooled plasma from US donors (PP-US) was also obtained from Omrix.

**Passive transfer of mouse anti-WNV hyperimmune serum or human immunoglobulins.** Four-week-old BALB/c mice received ip injections of 0.2 mL of serum, PP, or IVIG before or after WNV infection, according to the experimental protocol. Clinical signs that precede death include ruffling fur, weight loss, hunchback posture, and hind-limb paralysis. Because mice demonstrate age-dependent susceptibility to the development of fatal WNV disease, we first evaluated the susceptibility and kinetics of this viral infection in 4-week-old female BALB/c mice. Mice were infected ip with 1000 pfu (200 LD₅₀) of virus, and viral replication in blood and brain was monitored. Detectable virus titers (2 × 10⁴ pfu/mL) appeared in the blood as early as day 1 after inoculation (figure 1). Viral replication reached a peak of 3 × 10⁵ pfu/mL by day 2 and decreased slowly thereafter. The transient viremia lasted for ~6 days. After day 6, virus titers in the blood dropped below the level of detection of our plaque assay. Twenty-four hours after viral replication in the blood reached its peak, detectable virus titers appeared in the brain. In this organ, a dramatic, steep, and quick increase in virus titers was observed, reaching a high level of 10⁶–5 × 10⁵ pfu/brain by day 6–7 (figure 1). At this point, deaths began to occur, and the mortality rate was 100% by day 11.

**Protection against a fatal WNV infection by passive transfer of human IVIG or human PP.** The aim of our passive transfer experiments was to examine whether adoptive transfers of IVIG or human PP protect mice from the development of fatal WNV infection. In these experiments, we tested the protective efficacy of IVIG-IL, IVIG-US, PP-IL, and PP-US (described in Materials and Methods). We compared the protective potential of these human preparations to that of mouse anti-WNV hyperimmune serum. Four-week-old mice were injected ip with 100 pfu/mouse (20 LD₅₀) or 1000 pfu/mouse (200 LD₅₀) and were treated ip 1 day before and on days 1 and 3 after inoculation with 0.2 mL of (1) undiluted mouse anti-WNV hyperimmune serum, (2) normal mouse serum, (3) IVIG-IL, (4) IVIG-US, (5) human PP-IL, and pooled plasma from US donors (PP-US) was also obtained from Omrix.

**RESULTS**

**Time course of WNV replication in blood and CNS in WNV-infected mice.** WNV is a neuroinvasive flavivirus that causes CNS infection, paralysis, encephalitis, and death in mice [31].
Table 1. Protection of West Nile virus (WNV)-infected mice by passive transfers of intravenous immunoglobulin (IVIG) or pooled plasma (PP).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival, % (no. of deaths/no. of treated mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse anti-WNV hyperimmune serum</td>
<td>100 (0/6) 100 (0/6)</td>
</tr>
<tr>
<td>Normal mouse serum</td>
<td>0 (6/6) 0 (6/6)</td>
</tr>
<tr>
<td>IVIG-IL</td>
<td>100 (0/10) 100 (0/10)</td>
</tr>
<tr>
<td>IVIG-US</td>
<td>0 (6/6) 0 (6/6)</td>
</tr>
<tr>
<td>PP-IL</td>
<td>100 (0/6) 100 (0/6)</td>
</tr>
<tr>
<td>PP-US</td>
<td>0 (6/6) 0 (6/6)</td>
</tr>
</tbody>
</table>

NOTE. Groups of 4-week-old BALB/c mice were treated intraperitoneally with mouse anti-WNV hyperimmune serum or with different preparations of undiluted IVIG or PP 1 day before and 1 and 3 days after intraperitoneal injection of 100 (20 LD₅₀) or 1000 (200 LD₅₀) pfu of WNV. Mice were observed daily for mortality for 21 days. IL, from Israeli blood donors; US, from US blood donors.

(5) PP-IL, or (6) PP-US. The results, summarized in table 1, show that passively transferred mouse anti-WNV hyperimmune serum conferred 100% protection on mice infected with 20 LD₅₀ or 200 LD₅₀ of virus, whereas no mice that received normal mouse serum survived. The same level of protection was achieved using IVIG-IL and PP-IL, whereas IVIG-US and PP-US showed no protective efficacy. Serum was collected individually from surviving mice 21 days after infection and tested for antibody titers by ELISA. All mice had high levels of anti-WNV antibody titers, ranging from 1:1600 to 1:3200 (data not shown). These results clearly show that all WNV-infected mice developed high and protective antibody titers as a result of passive transfer of IVIG.

Therapeutic effect on WNV infection of single or serial passive transfers of IVIG-IL. In another set of experiments, the therapeutic effect of single or serial treatments of undiluted IVIG-IL or PP-IL was investigated. Mice were infected with 1000 pfu/mouse ip and then received (1) a single injection of PP-IL or IVIG-IL 4 h after inoculation with virus, (2) a single injection of IVIG-IL 1 day after inoculation, (3) 2 injections of IVIG-IL on days 1 and 2 after inoculation, (4) 3 injections of IVIG-IL on days 1, 2, and 3 after inoculation, or (5) 5 daily injections of IVIG-IL on days 1–5 after inoculation. As shown in table 2, a single injection of PP-IL or IVIG-IL 4 h after inoculation protected 95%–100% of WNV-infected mice from the development of fatal infection. This protection decreased to 64% when a single injection of IVIG-IL was administered 1 day after WNV inoculation. Protection increased to 75% when IVIG-IL was administered on days 1 and 2 and to 92% when a third injection of IVIG-IL was added on day 3 after inoculation. Five daily injections of IVIG-IL, administered on days 1–5 after virus inoculation, protected 100% of the infected mice. Mice inoculated only with WNV developed encephalitis 7–8 days after infection, as expected, and died between days 8 and 11. In mice treated with IVIG-IL that did not survive (treatment regimens 2, 3, and 4), the onset of disease and death was delayed by 3–4 days, compared with the WNV-infected untreated controls. No signs of CNS infection were observed in surviving IVIG-treated mice.

Dose-dependence of IVIG-IL therapy. To study whether the therapeutic effect of IVIG-IL is dose dependent, we treated mice with 0.1, 1, or 10 mg of IVIG-IL 4 h after infection with 100 or 1000 pfu of WNV/mouse. The results, summarized in figure 2, demonstrate that administration of 10 mg of (undiluted) IVIG-IL protected 100% of mice infected with 100 or 1000 pfu of WNV. Treatment with 1 mg conferred full protection only to mice infected with 100 pfu of WNV, and 80% of mice infected with 1000 pfu of virus survived. Therapy with 0.1 mg protected 70% of the mice infected with 100 pfu of WNV, and none of the mice infected with 1000 pfu survived. The antibody treatment delayed the mortality in this group by 2 days (data not shown).

Effect of high-dose therapy on WNV infection. To study the ability of IVIG to protect animals for prolonged periods after infection, mice were injected with 100 pfu of WNV, and a dose of 20 mg of IVIG-IL was used for treatment. This dose was administered on days 1, 1 and 2, 2 and 3, or 3 and 4 after WNV infection. As shown in figure 3, administration of a single injection of 20 mg of IVIG-IL 1 day after infection protected 80% of the infected mice, and full protection was achieved with 2 treatments administered on days 1 and 2 or 2 and 3 after infection. Five daily injections of IVIG-IL administered on days 1–5 after virus inoculation protected 100% of the infected mice. Mice inoculated only with WNV developed encephalitis 7–8 days after infection, as expected, and died between days 8 and 11. In mice treated with IVIG-IL that did not survive (treatment regimens 2, 3, and 4), the onset of disease and death was delayed by 3–4 days, compared with the WNV-infected untreated controls. No signs of CNS infection were observed in surviving IVIG-treated mice.

Table 2. Therapeutic effect of a single or serial injections of intravenous immunoglobulin (IVIG) and pooled plasma (PP) on West Nile virus infection.

<table>
<thead>
<tr>
<th>Treatment, time of treatment</th>
<th>No. of deaths/ no. of treated mice</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>12/12</td>
<td>0</td>
</tr>
<tr>
<td>PP-IL, 4 h</td>
<td>0/12</td>
<td>100</td>
</tr>
<tr>
<td>IVIG-IL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>1/18</td>
<td>95</td>
</tr>
<tr>
<td>1 day</td>
<td>5/14</td>
<td>64</td>
</tr>
<tr>
<td>1 and 2 days</td>
<td>3/12</td>
<td>75</td>
</tr>
<tr>
<td>1, 2, and 3 days</td>
<td>1/12</td>
<td>92</td>
</tr>
<tr>
<td>1, 2, 3, 4, and 5 days</td>
<td>0/14</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. Groups of 4-week-old BALB/c mice were treated intraperitoneally (0.2 mL/mouse) with PP-IL or IVIG-IL at different times after intraperitoneal injection of 1000 pfu of West Nile virus. Mice were observed daily for mortality for 21 days. IL, from Israeli blood donors; US, from US blood donors.

* Time after infection at which treatment was administered.
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Figure 2. Dose-dependent effect of intravenous immunoglobulin (IVIG) therapy. Groups of 4-week-old BALB/c mice were treated intraperitoneally with different amounts of IVIG from healthy Israeli donors (IVIG-IL) 4 h after injection of 1000 (gray columns) or 100 (white columns) pfu of West Nile virus. Mice were observed daily for 21 days for death.

Figure 3. Survival among West Nile virus-infected mice after treatment with immunoglobulin. Groups of 4-week-old BALB/c mice were treated intraperitoneally with 20 mg/mouse of intravenous immunoglobulin from healthy Israeli donors 1 day (black diamonds), 1 and 2 days (white squares), 2 and 3 days (black triangles), or 3 and 4 days (black circles) after injection with 100 pfu of West Nile virus. One group of infected mice received no treatment (control; white circles).

infection. Treatment on days 3 and 4 resulted in 50% protection. In this group, death was delayed in the IVIG-treated mice that ultimately did not survive.

Effect of IVIG-IL therapy on viral replication in infected mice. Virus titers in the blood and brains of mice that received 1 injection of 0.2 mL of undiluted IVIG-IL (10 mg/mouse) 4 h after injection of virus were measured and compared with those of untreated WNV-infected mice. Mice were individually killed, and titers were determined on days 2 and 3 in blood and on day 8 in brains. As shown in table 3, no infectious virus could be detected in blood or in the brains of IVIG-IL–treated WNV-infected mice, whereas in untreated WNV-infected mice, virus was detected in every mouse. All mice had virus titers in blood of $1 \times 10^7$ pfu/mL on day 2 and $3 \times 10^7$ pfu/mL on day 3 and in the brain of $1 \times 10^6$ pfu. In groups in which mortality was observed, 100% of untreated WNV-infected mice died, and 100% of IVIG-IL–treated WNV-infected mice survived.

DISCUSSION

In the present study, we used the murine model of WNV infection to evaluate the protective efficacy of IVIG for treatment of this viral infection. WNV causes a systemic infection in mice and invades the CNS, resulting in death in 1–2 weeks [31–33]. We found that the time course of the development of viremia and penetration of the brain by this virus directly correlated with the size of the infecting dose. In mice infected with 200 LD$_{50}$ virus was detected in the blood as early as day 1 after infection, penetration into the CNS occurred on day 3, and by days 8–11, mortality was 100%. A delay of 3–5 days in the kinetics of viral replication in the brain, brain penetration, and death was observed in mice inoculated with 20 LD$_{50}$. This dose killed 100% of infected mice between days 10 and 14 (data not shown).

Mice infected with 2 doses of 200 LD$_{50}$ or 20 LD$_{50}$ pfu were treated with IVIG-IL, PP-IL, IVIG-US, or PP-US 1 day before and 1 and 3 days after virus. The Israeli blood products protected 100% of mice infected with high and low viral doses, but the US blood products afforded no protection. The differences in the protective efficacy of the Israeli and the US blood products probably reflect the differences in the geographic distribution of WNV before its introduction to the US in 1999. Because this virus is endemic in Israel and the Middle East, the adult population developed natural immunity to the virus, whereas the US adult population did not begin to develop immunity to WNV until 1999. The US blood products used in the present experiments were obtained before the appearance of WNV in the Western Hemisphere.

The therapeutic efficacy of passive transfer of IVIG-IL was examined in another series of experiments. The results of those experiments clearly indicate that there is a linear correlation between the amount of IVIG-IL used for treatment and the level of protection and that there is an inverse correlation between virus load and the protective efficacy of passive transfer.

There is a mounting body of evidence to support the pivotal role of antibodies in the clearance of flavivirus infections [19–22, 41]. It has been shown that passive transfer of monoclonal or polyclonal virus-specific antibodies can protect the host from infection and have a therapeutic effect on an already-established infection. The protective effect of passively transferred antibodies has, in most cases, been attributed to the
ability of the antibodies to neutralize virus, and indeed, in some experimental systems, a direct correlation was found between in vitro neutralization activity and in vivo protective efficacy [23, 42, 43]. As demonstrated in the present study, the efficiency of the protection by passive antibodies was directly related to the amount of antibodies applied and to the time and dose of the infecting virus [23, 42]. Like other researchers [23, 44], we found that antibody treatment was most effective in controlling the viremic phase of the infection. Nonetheless, because effective treatments were demonstrated at times when viral replication has already taken place in the brain, it is impossible to rule out completely the possibility that antibody penetration to the brain occurs, as has been shown by Griffin et al. [45] in the case of Sindbis virus infection.

Whether the protective efficacy of antibodies is directly correlated to their ability to neutralize virus also is not clear, because studies involving several viruses, including flaviviruses, have shown that clearance of infectious virus can result from direct suppression of intracellular viral replication by antibodies [45–47]. It is therefore possible that the therapeutic effect of virus-specific antibodies is the result not only of neutralization of extracellular virus but also of suppression of intracellular viral replication.

It is important to note that no viral infectivity in blood or brain could be detected in the IVIG-IL–treated WNV-infected surviving mice at the same time that viral replication reached high titers in the untreated WNV-infected mice. Although no viral infectivity could be detected in the IVIG-IL–treated mice that had survived, high antibody titers of $>1:3200$ were detected by ELISA 21 days after infection. This titer is of the same order of magnitude as that obtained using hyperimmune serum prepared by immunizing mice with a sublethal dose of WNV. Similar observations were made by Gupta et al. [42], who demonstrated that the efficacy of passive antibody treatment against Ebola virus infection is a result of suppression of viral growth that allows the development of immunity. Furthermore, studies of hemorrhagic fever [48] and MVEV infection [24] showed that passively transferred IgG protected 100% of mice and allowed priming of the immune response to provide long-term immunity against subsequent infections [24, 48]. Whether, in the case of WNV infection, the IVIG-IL treatment leads to the development of a persistent infection that elicits lifelong immunity has yet to be determined.

Passive transfer of IVIG is a well-established procedure that has been extensively used as replacement therapy since antibody deficiencies first were recognized [30]. γ-globulins were used successfully to protect against a number of viral infections, including infection with varicella virus [49], coxsackievirus [50], and parvovirus [51] and viral encephalomyelitis [52].

Human IVIG from Israeli donors was prepared from a pool of blood samples collected from at least 1000 healthy blood donors in the years 1999–2000. This IVIG preparation has been approved by the US Food and Drug Administration for clinical use and is routinely administered for treatment of patients suffering from a variety of diseases, including multiple sclerosis, myasthenia gravis, idiopathic thrombocytopenia purpura, and inflammatory demyelinating polyneuropathy. Furthermore, this IVIG preparation was successfully used for the treatment of 2 Israeli patients with immunosuppression who had West Nile fever [53, 54]. Our results provide further support for the validity of this treatment for West Nile fever. This is particularly important in view of the present lack of effective therapy for this emerging viral infection.

References


