Recovery from a severe West Nile Virus infection in a one-year-old stallion following interferon alpha-2b treatment: an equine model for human therapy

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Abstract

West Nile Virus (WNV) is a disease that affects both people and horses as dead-end hosts in a similar manner. Transmitted through the infected bite of a mosquito, manifestation of the disease ranges in severity from being asymptomatic to causing severe encephalitis. Therapy consists largely of supportive care, but the use of antiviral medication, such as interferon alpha-2b (INFa-2b), has been hypothesized to improve outcomes in equine cases. This case report highlights the possible benefits of administration of INFa-2b in the case of a severely neurologic young stallion infected with WNV. Greater understanding of the association of INFa-2b therapy with the outcome of equine WNV cases may provide insight into its potential use in the therapy of human WNV cases.

Background

West Nile Virus is a positive-sense, single-stranded RNA arbovirus within the genus Flaviviridae that is transmitted through the bite of an infected *Culex sp.* mosquito. Birds are the natural amplifier host of WNV, but the virus may also be transmitted to mammals via mosquito bite. Horses and people are dead-end hosts; they may contract the disease and become clinically symptomatic, but they cannot transmit the disease. Once bitten by an infected mosquito, the incubation period of the virus is 2 to 15 days.[1] Systemic infection results in flu-like symptoms, ataxia, paresis, and, in severe cases, encephalitis. Additional symptoms noted in equine cases include muscle fasciculations of the muzzle, eyelids, head, neck, and trunk, and increased aggression.

A Food and Drug Administration-approved vaccine for WNV in horses is recommended to be administered annually or biannually based on geographic location as standard of preventative care. Once a horse has become infected, medical care is largely supportive. Mortality risk typically ranges from 22 to 30%; however, once a horse becomes laterally recumbent, the mortality risk increases to 71%.[2] The standard for therapy in equine cases consists of three elements: antiviral medication, systemic anti-inflammatory medication, and supportive care. The goal is to decrease pain and discomfort while resolving the viral infection. Supportive care consists of IV fluids, limb bandages, gastroprotectants, and prophylactic antibiotics. Flunixin meglumine is considered the drug of choice as a visceral anti-inflammatory medication. Antiviral medication may consist of either INFa-2b, through activation of the innate immune response, or hyper-immune equine WNV plasma.

INFa-2b activates the innate immune response through upregulating and activating antiviral proteins such as RNA-activated protein kinase and RnaseL.[3] INFa-2b also modulates the adaptive immune system and can prolong cell life. Studies have shown INFa-2b prolonged survival of astrocytes and neurons despite deprivation of growth factors.[3] This perseverance of the neural cell population is thought to aid in limiting CNS damage during a viral infection.

Continued investigation into potential methods to control WNV in people, such as an effective vaccine or targeted biologic, has yet to show consistent efficacy in clinical trials.[4,5] At present, preventative measures consist solely of mosquito control and environmental management. Therapy for symptomatic cases in people is, like in horses, also largely supportive. Use of antiviral medications has shown promise in *in vitro* studies,[6] but is not yet approved or use in human cases. The purpose of this case report is to highlight the use of INFa-2b in a severe case of WNV displayed in a one-year-old stallion and discuss its use as a treatment in people.[7]

Interferons were first described in 1957 as cellular products that interfere with viral infection.[8] Over the next 40 years of research, INFa was found to have immunomodulatory, anti-

proliferative, and antiviral properties. The genes coding for INFa are located on the ninth chromosome in people and code for a polypeptide chain 165-166 amino acids in length.[8] The human INFa-2b is a glycoprotein, 166 amino acids in length, that activates the Janus activated kinase/signal transducer activation of transcription (JAK-STAT) pathway through phosphorylation.[8] This pathway plays a key role in cell growth regulation, apoptosis, and cell differentiation.

INFa-2b has been used in people as a therapy for Hepatitis C infection and many cancers. It has been approved by the FDA as a monotherapy or in conjunction with other chemotherapeutics for melanoma, leukemia, follicular lymphoma, and renal cell carcinoma.[8] It upregulates p53 response rate to stress signaling and can initiate apoptosis through the tumor necrosis factor alpha (TNFa) signal transduction pathway.

Murine studies, in which INFa-knockout mice and wild-type mice were infected with WNV, have shown that INFa-2b increases the innate immune response to the virus and decreases viral replication.[3,9] The knockout mice showed a higher viremia with increased viral burden in peripheral tissues and 100% mortality in approximately three days.[3] Analysis of neural tissues from the knockout mice showed higher titers to WNV and increased neuronal cell death when compared to the wild-type mice.

Case Presentation

A one-year-old stallion presented to the KSU Veterinary Health Center with a one-day history of suspected colic. On presentation, he was ataxic and had difficulty standing and walking. Despite treatment with IV fluids, limb bandages, omeprazole paste (2 mg/kg by mouth daily), and flunixin meglumine (1.1 mg/kg IV daily), two days after presentation he progressed to lateral recumbency with an inability to stand.

Diagnostic tests included cervical vertebral radiographs, cerebrospinal fluid (CSF) analysis, and submission of the CSF for WNV ELISA, Eastern Equine Encephalomyelitis IgM

capture ELISA, and Western Equine Encephalomyelitis IgM capture ELISA. Cervical radiographs were unremarkable and had no evidence of cervical vertebral myelopathy. CSF analysis revealed a mononuclear pleocytosis consistent with a viral infection. The WNV ELISA test was positive.

Due to the stallion's advanced disease, aggressive therapy was initiated with 3 million units of INFa-2b administered subcutaneously once daily. Previous supportive therapy was continued with addition of doxycycline (10 mg/kg PO q12h)-, gabapentin (10 mg/kg PO q8h), sucralfate (4.5 mg/kg PO q6h), reserpine (2 mg/kg PO daily), and vitamin E supplementation (6 IU/kg PO daily). The patient developed numerous superficial skin ulcerations due to lateral recumbency. These were treated with topical gentamicin spray and routine bandage changes. He also developed a superficial corneal ulcer of the left eye that resolved after treatment with ofloxacin, and atropine administered through a subpalpebral line every six hours. A sling was employed to help support standing for short periods of time 3 to 4 times daily.

After 14 days of recumbency and aggressive therapy, the stallion was able to stand without assistance. He was discharged 35 days after admission substantially improved and able to walk unassisted.

Discussion

The presented case details the full recovery from WNV of a young stallion following aggressive therapy which included the use of the potent antiviral INFa-2b. Given that horses and people are dead-end hosts of WNV, the use of INFa-2b in this equine case provides a One-Health perspective for the potential use of INFa-2b as an adjunct therapy for WNV infections in humans. Interestingly, while INFa-2b is a component of the standard of care for WNV in equine medicine, use of INFa-2b in WNV infected people has only been documented in a limited number of cases and remains a controversial therapy due to its variability in success. [10,11]

Several case reports have been published detailing the use of INFa-2b in treatment of human WNV encephalitis.[10] In the two cases described, prior to administration of INFa-2b, the patients were disoriented with an inability to respond to verbal commands and had progressed to an obtunded state. On day-three after the onset of neurological signs, daily subcutaneous administration of 3 million U of INFa-2b was initiated. After the second day of administration, both patients' mental status was greatly improved. INFa-2b therapy continued for 14 days and both patients were discharged from the hospital. Serial follow-up appointments showed continued improvement and complete resolution of symptoms at one year.

In another case, a 26-year-old female was diagnosed with WNV encephalitis.[11] She presented with paraparesis and fecal/urinary retention. She was administered the same protocol of INFa-2b on day 7 after onset of neurological signs. Four weeks post therapy, the paraparesis did not improve but the fecal/urinary retention resolved and sensory function to the lower limbs had improved. The differences in outcome between these cases may suggest that there is a critical window for administration of INFa-2b therapy. Furthermore, decreased responses to repeated therapy may be due to production of anti-INFa-2b antibodies by the patient's immune system. This has been reported in people and calves.[12]

Despite the varying results of INFa-2b therapy in people, the hypothesis that timely administration of exogenous INFa-2b may help mediate the detrimental effects of the virus is based on the observation that WNV indirectly inhibits the INF signaling pathways that lead to activation of the cell-mediated immune response.[13] Since people and horses have similar biologic responses to WNV, further study into the use of INFa-2b as a first-line therapy, at early onset of neurologic signs, is warranted.

Learning Points

- Standard for therapy in equine cases consists of three elements: antiviral medication, systemic anti-inflammatory medication, and supportive care

- INFa-2b activates the innate immune response
- Timely administration of exogenous INFa-2b may help mediate the effects of WNV

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