Focus

Efficacy of Prophylactic and Therapeutic Human Immunoglobulin on West Nile Virus Infection

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The murine model of West Nile virus was used by Ben Nathan et al. [1] to evaluate the prophylactic and therapeutic efficacy of pooled human plasma and intravenous human immunoglobulin (Omrigan, Omrix Biopharmaceuticals, Ness Ziona, Israel) on this virus infection. The studies were initiated following reports published after the West Nile fever epidemic in Israel in 2000 that showed some improvement in patients treated with the Israeli IVIG [2,3].

West Nile virus causes a systemic infection in mice and invades the central nervous system, resulting in death 1–2 weeks later. Mice infected with two doses of 200 LD_{50} or 20 LD_{50} PFU/mouse received one to six treatments with Israeli pooled human plasma or IVIG, or American pooled plasma or IVIG, before and after virus infection. While the Israeli blood products protected 100% of mice infected with both high and low viral doses, the U.S. blood products afforded no protection.

The results of these experiments showed that any treatment containing specific antibodies yielded high rates of survival. In addition, they indicated that the efficiency of the protection by passive antibodies was directly related to the amount of antibodies applied, as well as to the time and dosage of the infecting virus. Similar to other reports, it was also found that the antibody treatment was most effective in the control of the viremic phase of the infection. Nonetheless, it was impossible to completely rule out antibody penetration to the brain, as was shown by Griffin et al. [4] in the case of Sindbis virus infection.

It is also not clear whether the protective efficacy of the antibodies is directly correlated to their ability to neutralize virus since studies using several viruses, including flaviviruses, have shown that clearance of infectious virus can also result from direct suppression of intracellular virus replication by antibodies [4–6]. It is therefore possible that the therapeutic effect of the specific antibodies occurs not only by neutralization of extracellular virus but also by suppression of intracellular viral replication.

The Israeli human IVIG was prepared from a pool of at least 1,000 healthy blood donors collected in the years 1999–2000. This IVIG preparation has been approved by the U.S. Food and Drug Administration for clinical use and is being routinely administered for the treatment of patients suffering from a variety of diseases, including multiple sclerosis, myasthenia gravis, idiopathic thrombocytopenia purpura and inflammatory demyelinating polyneuropathies. The results provide further support to the validity of this treatment for West Nile virus. This is particularly important in view of the present lack of effective therapy for this emerging virus infection.

The article published by Ben Nathan and colleagues [1] was followed by an editorial by Agrawal and Peterson [7]. In their editorial the authors raise some critical questions but nonetheless support the IVIG

IVIF = intravenous immunoglobulin

treatment since it has no side effects compared to the other candidate therapies of ribavirin and interferon. Agrawal and Petersen [7] encourage the start of clinical trials, this being the only way to know whether the "results in animals will translate to significant benefits in humans."

Note: Omrix just signed a contract with the U.S. National Institutes for Health for a multicenter clinical trial of their IVIG product, which was also approved by the FDA.

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Addendum: On 9 September, USA TODAY reported: "A study sponsored by the National Institute of Allergy and Infectious Diseases is now enrolling patients already infected with West Nile to see if intravenous infusions of antibodies, substances produced by the immune system to fight infection, will prevent death or brain damage. The clinical trial will enroll about 100 patients who are hospitalized and have West Nile encephalitis or are at risk of developing it." The Institute's Director, Dr. Anthony Fauci, stated: "Currently, clinicians can provide only supportive care for patients infected with WNV. We hope that the results from this study will ultimately give physicians and their patients a useful treatment option."