Ganciclovir for the Treatment of Congenital Cytomegalovirus

What are the Side Effects?

To the Editors:

Congenital cytomegalovirus (CMV) infection can cause significant neurologic morbidity. Studies have shown that antiviral therapy with ganciclovir (GCV) or valganciclovir (V-GCV) improves hearing and neurodevelopmental outcomes. Counseling parents about the benefits and potential adverse effects of antiviral therapy is essential. We reviewed the published literature to determine the rate of adverse effects when GCV/V-GCV is used for the treatment of congenital CMV.

In June 2013, EMBASE and Medline were searched using the following key words: Ganciclovir, Antiviral agents, Cytomegalovirus, Infant, Newborn, Newborn* or Neonat*. Studies including 10 or more neonates were included. Seven studies were identified.

Neutropenia was the most commonly reported side effect of GCV although the definition varied between studies. Two retrospective studies found that between 46% and 52% of treated infants developed neutropenia.[1,2] In most cases, the absolute neutrophil count remained >500 cells/mm^3 with the exception of 2 of 12 neonates in 1 study.[2] A similar rate of neutropenia (63%) was reported in a randomized-controlled trial (RCT) of 46 neonates treated with 12 mg/kg/day GCV.[3] In contrast, neutropenia occurred less frequently (2 of 12 infants) when children >30 days of age were treated for 3 weeks with a dose of 10 mg/kg/d.[4] The frequency of neutropenia was not affected by GCV dose in 2 further RCTs.[5,6] There are limited data on V-GCV side effects; 1 prospective study of 6 weeks of V-GCV reported borderline neutropenia in 1 of 13 neonates.[7] Neutropenia generally responded to dose adjustment[1] or G-CSF,[7] but some patients required treatment discontinuation.[6]

Four studies described hepatotoxicity. Two studies, including a total of 55 children, found that hepatotoxicity occurred in 30% of infants treated with GCV 8 mg/kg/d, GCV 12 mg/kg/d or V-GCV 16 mg/kg/d.[1,6] Another small RCT of 12 infants reported higher rates of hepatotoxicity in those treated with GCV 15 mg/kg/d compared with those receiving a lower (10 mg/kg/d) dose (33.3% vs. 0%).[5] In contrast, no hepatotoxicity was reported in a study of 25 neonates treated with 12 mg/kg/d GCV for 6 weeks.[3]

Thrombocytopenia (platelets <50,000 cells/mm^3) was observed in approximately one-third of children treated with GCV in 1 RCT that compared different GCV doses.[6] The frequency of thrombocytopenia was not dose related. A prospective study of 13 infants found 1 that required treatment discontinuation due to thrombocytopenia.[7] This infant had a low platelet count at birth and it is not possible to ascertain the relative contribution of CMV and GCV to the thrombocytopenia. In contrast, no thrombocytopenia was observed with GCV treatment in 2 RCTs.[3,5]

A raised serum creatinine was not seen in any of the studies reviewed, though 1 used a high upper limit for creatinine (> 2 mg/L).[3,5,6] The frequency of central line infections associated with intravenous access was reported at 8.7% and 10.3% in 2 studies of 6 weeks GCV.[2,3] In animal studies, GCV use has been associated with infertility but this has not been studied in humans.[8]

Overall, our review highlights that adverse effects are common in neonates treated for congenital CMV infection. Neutropenia occurs in approximately half of infants but is rarely severe and usually resolves with dose adjustment or treatment discontinuation. Hepatotoxicity and thrombocytopenia are also relatively common, occurring in up to 30% of treated infants. Our data will aid clinicians in counseling parents about the pros and cons of antiviral treatment.

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Neurotrichinosis in a Pediatric Patient

To the Editors:

Neurotrichinosis is an infrequent but severe form of trichinosis. Pediatric neurotrichinosis reports in the medical literature are scarce and mostly outdated.

We report a case of neurotrichinosis in a 14-year-old girl from a rural area in Argentina (province of La Pampa). The patient presented with a history of intermittent fever, fatigue and

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myalgia for 1 month before admission to the hospital, associated with progressive loss of function of the lower limbs. She had no significant previous medical history and had normal neurologic development. All the other members in her household were asymptomatic.

The initial physical examination revealed an afebrile, sick-looking child, with weakness of the soft palate, left facial hemiparesis and bilateral brachiocrural hemiparesis, exhaustible clonus and loss of abdominal reflexes. Blood tests showed leukocytosis with severe eosinophilia (4500/mm^3), elevated creatine phosphokinase (164 IU/mL) and lactate dehydrogenase (460 IU/mL), without other significant findings. Cerebrospinal fluid analysis was normal, and blood and cerebrospinal fluid cultures were negative for bacteria and fungi. Eye and cardiologic examinations and abdominal and muscle ultrasound examinations were normal. *Trichinella spiralis*-specific serology (enzyme-linked immunosorbent assay) was positive. On further questioning, the patient remembered intake of undercooked homemade pork products (charcuterie) 2 weeks before onset of symptoms. No other members of her family had ingested the products, explaining the lack of symptoms in the rest of the household.

Brain computed tomography (CT) revealed hypodense, multifocal, small lesions in the cortex and white substance consistent with ischemia; magnetic resonance imaging (MRI) showed multifocal lesions hypointense in T1-weighted images and hyperintense in T2-weighted images. (Fig. 1)

The patient was treated with oral albendazole, 800 mg/day in 2 daily doses for 5 days, and oral methylprednisone, 1 mg/kg/day in 2 daily doses for 10 days. Within 4 days of treatment, muscle strength, hemiparesis, motility of the soft palate improved and muscle enzymes decreased in blood. After a week of treatment, myalgia receded and she was able to walk again. One month post-treatment, the patient was back to her normal activities, without sequelae; the follow-up CT showed full recovery.

Trichinosis is caused by infection with the larvae of *T. spiralis* due to the ingestion of undercooked, contaminated meat (mainly pork, horsemeat and game). An estimated 10,000 cases of trichinellosis occur every year worldwide, with a death rate of 0.2%, according to reports from 55 countries where trichinellosis occurs autochthonously.[1]

The diagnosis of trichinosis is based on epidemiology, clinical manifestations, laboratory, serological tests and imaging (CT or MRI).[1–3] Eosinophilia frequently appears 10 days after infection, peaking at the third or fourth week, followed by a gradual decline over months. Myositis, marked by myalgia and increased muscle enzymes in blood, is a common finding.[1,4] Neurotriquinosis is a rare complication, characterized by altered level of consciousness and, frequently, somnolence and apathy. Anisocoria, facial nerve paresis and Babinsky's reflexes have also been observed in severe cases.[1,5]

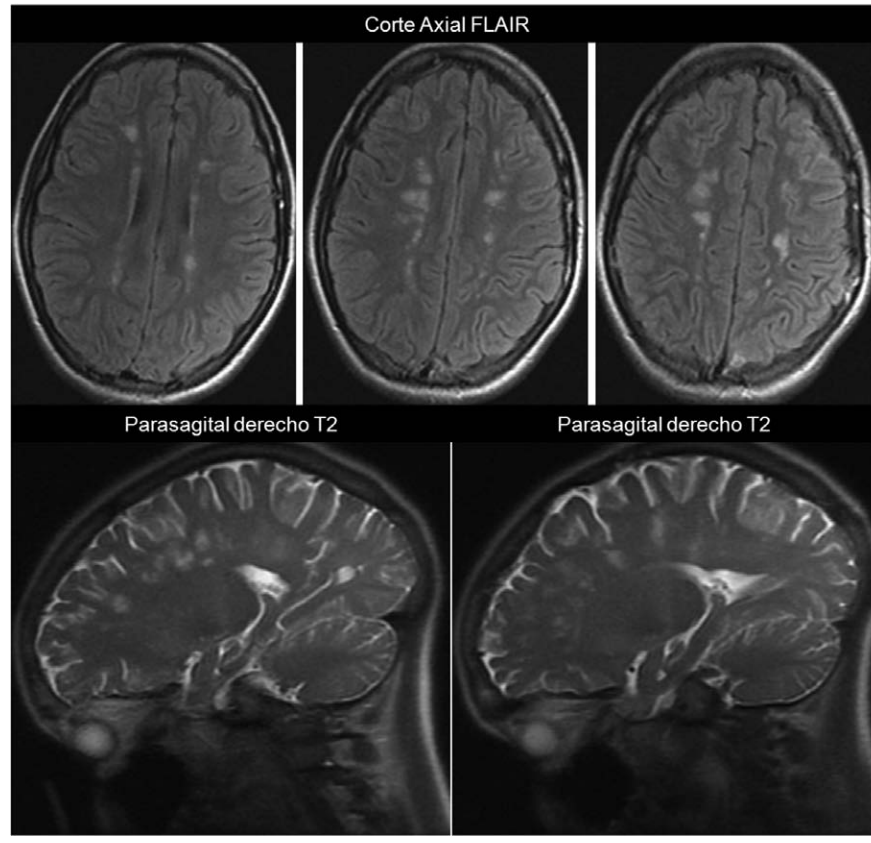

FIGURE 1. Brain MRI showed hypodense focal lesions in the white substance and in the periependymal region that enhance with contrast, without mass effect.

Our patient had central nervous system involvement evidenced by weakness and lesions consistent with ischemia in CT and MRI. Central nervous system localization is a rare but serious presentation and limited cases were reported,[5,6] with few pediatric reports. Signs of central nervous system infection are evident in the phase of larval migration or tissue invasion, which begins at the end of the second week of illness and persists for 4 weeks.

Several mechanisms have been proposed as responsible for the development of brain lesions, including cerebral blood vessels obstruction by larvae, cysts or granulomas, inflammation of brain parenchyma and reactive vasculitis with secondary thrombosis and infarction.[2,7–9]

As observed in our patient, treatment with corticosteroids rapidly improves myositis and vasculitis-related symptoms and prevents complications. Steroids should always be administered in combination with antihelmintics such as albendazole.[2,4] In our patient, we observed clinical improvement after 4 days of treatment.

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Measles Vaccine Strain From the Skin Rash of a DiGeorge Patient Receiving Tumor Necrosis Factor Inhibitor

To the Editors:

Isolation of measles virus has typically been from respiratory, blood or urine specimens, but identification from the skin has not been documented. We describe the first known case of measles vaccine-associated disease in a DiGeorge patient on tumor necrosis factor inhibitor therapy in which genotype A Edmonston vaccine strain virus was identified from skin scrapings of the patient's rash.

A 12-year-old boy was admitted to our hospital with a 2-day history of tactile fevers, sore throat, rash and conjunctivitis. Ten days earlier, he had inadvertently received the measles, mumps, rubella and varicella vaccine during a well-child visit. His past medical history was remarkable for DiGeorge syndrome, repaired Tetralogy of Fallot and juvenile idiopathic arthritis diagnosed at 15 months of age, which had been controlled for the past 5 years with weekly injections of the tumor necrosis factor inhibitor etanercept.

With the exception of live virus vaccines, he was otherwise up-to-date with his immunizations. He had recently undergone immune evaluation with a lymphocyte count of 1100×10^9 cells/L, of which the lymphocyte subsets were normal. The lymphocyte mitogen and antigen studies included low-normal responses to *Candida* and phytohemagglutinin and normal responses to tetanus, concanavalin A and pokeweed mitogen. Antibody titers to prior inactivated vaccines were normal.

After he developed the tactile fevers, his mother held further doses of etanercept, and he was directly admitted to the hospital. On admission, he was afebrile and appeared well. His examination was remarkable for mild conjunctivitis, palatal petechiae with posterior pharyngeal erythema and a blanching morbilliform rash that was present behind the ears, on the face, neck, back, chest and limbs. Mild post auricular cervical lymphadenopathy was present. There were no Koplik spots or vesicular lesions. Due to the possibility of an atypical varicella rash in a patient on a biologic immunomodulatory medication, intravenous acyclovir was initiated and the Minnesota Department of Health was notified. Scrapings of the rash were sent to evaluate for varicella zoster virus, and a urine sample and a buccal swab were collected for evaluation of measles virus.

Nucleic acids were isolated from the urine and skin samples using the Qiagen Viral RNA Mini Kit (Qiagen, Germantown, MD). Detection of measles virus was attained with a real-time TaqMan reverse transcription polymerase chain reaction targeting the nucleoprotein (N) gene.[1] Genotyping was determined following World Health Organization-recommended sequencing, which were aligned with CDC-designated reference sequences using MEGA5 software.[2] Both urine and skin samples were positive in triplicate for measles virus by reverse transcription polymerase chain reaction with 100% matched identity to each other and phylogenetically clustered as genotype A with Edmonston reference strain (AF266288). The buccal swab was inconclusive based on extraction control failure.

Although excretion of measles virus in his urine enabled detection and sequencing of the virus as a measles vaccine strain, the diagnosis of vaccine-associated disease was determined from the skin scrapings.[3] Measles virus is present in the skin rash during illness;[4] however, to our knowledge, this is the first reported measles vaccine case in which the vaccine strain was detected and genotyped from the skin rash.

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Challenges With New Rapid Influenza Diagnostic Tests

To the Editors:

Rapid influenza diagnostic tests (RIDTs) are often used at point-of-care due to their ease of use and rapidly available results. Most tests are lateral flow immunoassays that detect chromatographic changes if an influenza antigen is present in the respiratory specimen. These tests have high specificity (therefore, a positive is almost certainly a true positive) but low sensitivity (therefore, will often miss true cases).[1,2] A newer immunofluorescence assay, Sofia A+B FIA (Quidel, San Diego, CA), demonstrated increased sensitivity but maintained high specificity.[3] However, on December 3, 2012, Quidel issued a voluntary recall of certain lots of Sofia A+B because of false positive results.[4]

In August 2011, we began a prospective cohort study of children aged ≤36 months at Queen Sirikit National Institute of Child Health, the largest pediatric referral hospital in Thailand. Children (equal numbers of high risk and healthy) are followed for 2 years and parents contacted weekly to inquire about whether their child had acute respiratory illness. Ill children came to the hospital and had a combined nasal and throat swab collected and tested for influenza viruses by realtime reverse transcription polymerase chain reaction (rRT-PCR).[5]

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