Novel treatment (new drug/intervention; established drug/procedure in new situation)

Valganciclovir treatment of primary cytomegalovirus pneumonitis in an immunocompetent adult

Susan E Snape, Pradhib Venkatesan

Department of Infectious Diseases, Nottingham University Hospitals City Campus, Nottingham, UK

Correspondence to Dr Pradhib Venkatesan, pradhib.venkatesan@nuh.nhs.uk

Summary

Interstitial pneumonitis is a rare complication of cytomegalovirus (CMV) infection in the immunocompetent. There is a paucity of literature regarding treatment in these patients. A previously healthy, immunocompetent female patient presented with fever, shortness of breath, a dry non-productive cough and myalgia and was subsequently diagnosed with CMV interstitial pneumonitis. She was treated with valganciclovir and swiftly improved but experienced neutropenia, which resolved on treatment cessation.

BACKGROUND

Intravenous ganciclovir has been used in the treatment of immunocompetent patients with cytomegalovirus (CMV) pneumonitis. As far as we are aware, there are no other reports in the literature of the successful use of oral valganciclovir as treatment for CMV interstitial pneumonitis in an immunocompetent adult.

CASE PRESENTATION

A previously healthy 28-year-old female presented to her general practitioner with a 4-day history of fever, tender sinuses, bilateral frontal headache and a faint erythematous rash, which had resolved spontaneously after 2 days. Despite treatment with co-amoxiclav and then doxycycline for presumed sinusitis, she developed a dry, non-productive cough and myalgia rendering her bed bound. Her fevers continued. Therapy was switched to levofloxacin, but there was no improvement. After 2 weeks of illness she deteriorated with dyspnoea at rest, nausea and vomiting, precipitating hospital admission. She was previously fit and well and had no cardiovascular, genitourinary or neurological symptoms. She lived alone and had no travel history, sick contacts or pets. She smoked 20 cigarettes/day and had a new boyfriend of 2 months' duration. She drank less than 10 units of alcohol/week.

On presentation she was alert and orientated, flushed, pyrexial (39.4°C), tachycardic (135 beats/min) and dyspnoeic at rest (18 breaths/min), her blood pressure was 115/70 mm Hg, and saturations were 92% on 28% oxygen. Her throat was inflamed with no purulent exudate or tonsillar enlargement. Percussion note was resonant throughout the chest. On auscultation there was reduced air entry at both bases, but no crepitations or wheeze. Heart sounds, abdominal and neurological examinations were unremarkable. There was no lymphadenopathy or joint swelling.

Intravenous cefuroxime 1.5 g every 8 h and clarithromycin 500 mg every 12 h were commenced.

INVESTIGATIONS

Initial investigations revealed a normal urea, electrolytes, haemoglobin, white cell count and differential, and platelets and an erythrocyte sedimentation rate of 14 mm/h. Abnormal results are shown in table 1.

A chest radiograph showed consolidation in the medial segment of the middle lobe and in the anterior segment of the right upper lobe. CT pulmonary angiography excluded a pulmonary embolus but showed patchy consolidation of both lungs, more prominent on the right. Admission serology for CMV was reported positive for CMV IgM. Bronchoscopy was performed with no focal findings and a bronchioalveolar lavage obtained. Cytology showed a number of alveolar macrophages mixed with lymphocytes but no malignant cells. Immunofluorescence did not detect early antigen for CMV, influenza A and B, parainfluenza 1, 2 and 3, respiratory syncytial virus, *Chlamydia*, varicella zoster virus, *Legionella* or *Pneumocystis jiroveci* and viral culture was negative. No bacteria or mycobacteria were seen or isolated on culture. Acute and convalescent serum samples tested negative for *Legionella* and *Mycoplasma*. EBV serology was positive for IgM, IgG EBNA and IgG ELISA, indicating that there was past infection with EBV and likely non-specific cross-reactive antibodies present that reacted to the EBV IgM test. Autoantibody screening was negative except for IgG antinuclear antibodies, with a titre of 200 of uncertain significance. An HIV test was negative.

DIFFERENTIAL DIAGNOSIS

- Bacterial pneumonia
- Viral pneumonia
- Viral pneumonitis
- *Pneumocystis jiroveci* pneumonitis with underlying HIV
- Pulmonary mycobacterial infection
- Pulmonary embolism.

TREATMENT

The patient deteriorated further with increasing hypoxaemia, arterial blood gases on 8 l humidified O₂ showing pH

Table 1 Admission blood results

Test	Laboratory value	Normal range
C reactive protein	121 mg/l	0–10
Alkaline phosphatase	262 U/l	40–130
Alanine aminotransferase	152 U/l	0–45
γ -Glutamyl transferase	267 U/l	0–55
Albumin	23 g/l	30–50
D-dimers	1523 ng/ml	0–300
Arterial blood gases on air		
pH	7.48	7.36–7.44
pCO ₂	4.32 kPa	4.7–5.9
pO ₂	8.17 kPa	11–13

7.5, pCO₂ 3.91 kPa and pO₂ 7.68 kPa. The critical care outreach team was heavily involved and switched the patient to high flow O₂ at 70% and her pO₂ improved to 9.17 kPa. A serum CMV PCR result was obtained showing 46 764 copies/ml. A diagnosis of CMV pneumonitis was made. In view of the patient's deteriorating respiratory function and the likelihood of impending need for ventilatory support, the patient was started on valganciclovir 900 mg orally 12 hourly, with discontinuation of antibiotics as a last resort to prevent critical care admission. The response was marked – within 24 h the patient substantially improved, her oxygen requirements fell and from being bed bound she began to mobilise. Ten doses of valganciclovir were administered in total before the patient's neutrophil count fell to $0.76 \times 10^9/l$, whereupon the treatment was stopped. Her oxygen saturations were 92% on air. The patient was discharged 18 days after admission.

OUTCOME AND FOLLOW-UP

Outpatient review 2 weeks after discharge confirmed symptomatic improvement. The neutrophil count had risen to $1.14 \times 10^9/l$ and repeat CMV PCR did not detect CMV nucleic acid. Liver function tests had normalised. Pulmonary function tests, performed 9 weeks after hospital discharge, showed a forced vital capacity (FVC) of 3.15 (predicted value 3.6), a forced expiratory volume in 1 s (FEV₁) of 2.9 (predicted 3.2) and an FEV₁/FVC of 92 (predicted 83). Seven months later she had no respiratory symptoms and an unlimited exercise tolerance.

DISCUSSION

Asymptomatic CMV acquisition is common in immunocompetent individuals and by the fourth decade 40–100% of populations are seropositive. Severe CMV infection is rare in previously healthy individuals. Eddleston *et al*¹ reviewed the literature and identified 34 reported cases of severe CMV infection in immunocompetent individuals. Eight cases had pulmonary involvement. In view of the low prevalence of severe disease, it is unsurprising that the literature concerning treatment consists of case reports. A recent review by Cunha suggests CMV pneumonia in the immunocompetent is uncommon but is being recognised more frequently.² As CMV infection is usually self-limiting in the immunocompetent population, the role of antiviral therapy, with its potential side-effects of myelosuppression, renal toxicity, permanent infertility and teratogenesis, is questionable. However, Eddleston *et al*¹ reported that seven of 19 who survived had received ganciclovir

or foscarnet, whereas only one of 15 who died received potentially effective antiviral therapy. In several case reports the use of ganciclovir in severe cases was accompanied by rapid clinical improvement.^{3–6}

In immunocompromised adults, intravenously administered ganciclovir is advocated for severe disease. It is a nucleoside analogue and acts by causing termination of viral DNA elongation through competitively inhibiting the incorporation of deoxyguanosine triphosphate into DNA. The drug has activity against human herpes viruses, and is especially effective against CMV. Valganciclovir is an orally administered L-valine ester prodrug of ganciclovir. It has much improved oral bioavailability (60%) compared with oral ganciclovir (5%). Studies show valganciclovir is as effective as ganciclovir in prophylaxis and treatment of CMV disease in high-risk solid organ transplant recipients and in treatment of AIDS-related CMV retinitis.^{7–9} In the literature there are two reports of use of valganciclovir in the successful treatment of immunocompetent patients with gastrointestinal manifestations of CMV infection,¹⁰ and one report of CMV myopericarditis and hepatitis which rapidly responded to valganciclovir in an immunocompetent adult.¹²

Our patient had severe CMV pneumonitis. The decision to treat was driven by the level of hypoxaemia and the continuing decline of the patient. She responded swiftly to oral valganciclovir and avoided intubation and mechanical ventilation, and central line insertion for the administration of ganciclovir. The patient was treated for 5 days. However, our initial intention had been to treat for 21 days as although CMV pneumonitis is recognised as responding quickly to ganciclovir, in the immunocompetent patient the risk of relapse is present if there is an undefined underlying immune defect. Our patient did not relapse and was restored to full health by 7 months. As far as we are aware this is the first report of valganciclovir therapy in the treatment of CMV pneumonitis in an immunocompetent adult.

Learning points

- Severe cytomegalovirus (CMV) pneumonitis can occur in immunocompetent individuals.
- Oral valganciclovir can be used to treat severe CMV pneumonitis in immunocompetent adults.
- The use of oral valganciclovir circumvents the need for central line placement and the administration of intravenous ganciclovir.

Competing interests None.

Patient consent Obtained.

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