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Case report

Successful oral treatment of Ganciclovir resistant cytomegalovirus with Maribavir in the context of primary immunodeficiency: First case report and review

Philip D. Bright[a,*], Mark Gompels[a], Matthew Donati[b], Sarah Johnston[a]

[a] Immunology Department, North Bristol NHS Trust, Bristol, United Kingdom
[b] Public Health Laboratory, Public Health England, Bristol, United Kingdom

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1. Why this case is important

This case describes the first successful use of Maribavir in the treatment of Ganciclovir resistant cytomegalovirus (CMV) in a patient with combined primary immunodeficiency. Human primary CMV infection is often asymptomatic but may result in a glandular fever-like illness. After primary infection, CMV establishes latency and can reactivate periodically.

Generally, the first line treatment of CMV disease is Ganciclovir, which can most conveniently be administered as the oral prodrug Valganciclovir. Intravenous Foscarnet is usually the second line agent, but use is limited by nephrotoxicity and anaemia. In the context of resistance or toxicity from these medications other options, such as Maribavir, must be considered. Most of the evidence for CMV treatment is derived from patients with immunosuppression secondary to transplantation (solid organ or bone marrow) or HIV infection. These situations typically involve a changing (and usually improving) immune status, due either to a reduction of immunosuppressive treatment or effective HIV therapy, and CMV treatment is therefore usually only necessary for a short time. CMV infection in patients with persistent immunosuppression such as in primary immunodeficiency often requires long-term therapy, which risks development of viral drug resistance and severe drug toxicities. Further options for CMV treatment beyond oral Valganciclovir and intravenous Foscarnet, such as Maribavir, are therefore necessary in some patients with CMV disease.

2. Case description

A 61 year-old gentleman with a six-year history of diarrhoea to the Royal United Hospital in Bath, which had worsened with associated weight loss in the preceding six months, collapsed in March 2006. He had chronic sinusitis and a three-year history of productive cough, with multiple positive sputum cultures including *Haemophilus influenzae* and β-haemolytic Streptococcus. He was subsequently diagnosed with oesophageal candidiasis, CMV disease (viraemia plus histological confirmation on oesophageal and colonic biopsies), and a bacterial chest infection. No thymoma was evident on computerised tomography scanning.

Investigations for underlying immunodeficiency revealed negative HIV antibody/antigen and RNA tests, panhypogammaglobulinaemia with no paraprotein, low lymphocytes, and specialist tests for specific primary immunodeficiencies were negative.

His CMV disease was treated with 3 weeks of intravenous Foscarnet (60 mg/kg three times daily) followed by Valganciclovir (900 mg once daily). Valganciclovir was selected for reasons of convenience, improved compliance and avoidance of hospi-

* Corresponding author at: Immunology Department, Southmead Hospital, North Bristol NHS Trust, Dorian Way, Westbury-on-Trym, Bristol, BS10 5NB.
E-mail address: philip.bright@doctors.org.uk (P.D. Bright).

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tal admission, compared to intravenous Ganciclovir. As there was evidence of B-cell (panhypogammaglobulinaemia with recurrent respiratory infection with encapsulated bacteria) and T-cell deficiency (candidiasis, CMV disease), he was diagnosed with combined immunodeficiency and started on immunoglobulin replacement for antibody deficiency, with additional Co-trimoxazole prophylaxis.

The Valganciclovir was stopped after 3 months following negative blood CMV DNA viral load results associated with clinical recovery. He subsequently relapsed with CMV viraemia and diarrhoea suggestive of CMV colitis, and was effectively retreated with Valganciclovir (900 mg twice daily) for 3 weeks, followed by long-term Valganciclovir prophylaxis (900 mg once daily).

After 22 months of Valganciclovir prophylaxis, transient but recurrent low-level CMV viraemia developed, which resolved without treatment change. After a further 4 months he developed persistent CMV viraemia associated with intra-abdominal lymphadenopathy, and CMV disease was histopathologically evident on colonic and ileal biopsies. A Ganciclovir resistance mutation (UL97 mutation H520Q) was detected in CMV obtained from blood. He was treated with intravenous Foscarnet with good virological and clinical response, but developed severe penile ulceration. Subsequent treatment with intravenous Foscarnet resulted in similar ulceration necessitating pre-emptive catherisation. Cidofovir treatment (5 mg/kg daily) was tried with resultant temporary reduction in CMV viraemia but no clinical effect. High-dose intravenous Ganciclovir (10 mg/kg twice daily) was also ineffective. Oral Leflunomide (20 mg once daily) was started with some limited clinical and virological response.

Due to the complexity of the case and failure of adequate control of CMV, an application for compassionate use of Maribavir was made. Maribavir resulted in life-changing clinical improvement, an undetectable CMV viral load and no significant side effects. Maribavir was continued for 3 months, during which he remained very well, however ongoing drug funding could not be secured. The cost of Maribavir was £110,000 per annum with a potential discount available. This compares to a cost of Valganciclovir of £13,158 per annum, and Leflunomide of £747 per annum. Maribavir was therefore discontinued and Leflunomide reinstated with subsequent low-level CMV viraemia following the 2 months of treatment required for effective CMV treatment with Leflunomide. Fig. 1 shows his CMV treatment and CMV viraemia throughout, and Fig. 2 shows the specific response to Maribavir. The patient subsequently died in August 2012 as a result of complications following a splenectomy performed for haemolytic anaemia refractory to intravenous immunoglobulin.

Foscarnet treatments were for 3 weeks on each occasion. Viral loads were measured using an in-house modified PCR methodology [1] and were measured in copies/ml in whole blood.

3. Other similar and contrasting cases in the literature

Maribavir is an inhibitor of the CMV UL97 kinase and blocks the nuclear egress of CMV virions [2]. A placebo controlled study in preventing CMV disease following HSCT [3] involved three doses of Maribavir (100 mg twice daily, 400 mg once daily, 400 mg twice daily) and showed reduction in CMV disease in Maribavir groups compared to placebo. Further placebo controlled studies using low dose Maribavir (100 mg twice daily) to prevent CMV disease after engraftment following HSCT failed to show a difference in CMV disease between Maribavir and placebo [4], and following liver transplantation showed inferiority of Maribavir to Ganciclovir [5]. This failure could be attributable to the low dose used, the delay of treatment until after engraftment, or the exclusion of patients at high risk of CMV disease [4]. Use of Maribavir was then restricted to compassionate grounds. 12 of 18 patients who received Maribavir for treatment resistant CMV disease (400 mg twice daily) had a good response [6,7]. Two clinical trials have completed but have not yet been published looking to investigate Maribavir further, one in solid organ transplantation (SOT) and HSCT (http://clinicaltrials.gov NCT01611974), and the other preemptive therapy in SOT (EudraCT: 2010-024247-32).

4. Discussion on CMV treatment options

4.1. Standard therapies

4.1.1. Ganciclovir/Valganciclovir

Ganciclovir has poor oral bioavailability and is therefore predominantly given orally as its bioavailable prodrug Valganciclovir, the first-line anti-CMV treatment in most situations. Side effects including neutropenia, bone marrow hypoplasia, anaemia and thrombocytopenia [8].

4.1.2. Foscarnet

Foscarnet use is relatively limited by toxicity and it may cause electrolyte imbalances, nephrotoxicity, anaemia, and urogenital ulceration [8].

5. Alternative non-standard therapies to maribavir

5.1. Cidofovir/Brincidofovir (CMX-001)

Cidofovir is effective in CMV disease, but its use is complicated by significant nephrotoxicity and poor oral bioavailability. Brincidofovir is a phospholipid conjugate of Cidofovir with good bioavailability and reduced toxicity. Brincidofovir has been shown to be well tolerated and effective in preventing CMV events following haematopoetic stem cell transplantation (HSCT) [9], and was effective in a small case series of treatment for CMV after HSCT [10]. However, an unpublished phase III multicenter trial of Brincidofovir in preventing CMV infection in HSCT was unsuccessful (http://clinicaltrials.gov NCT01769170).

5.2. Letermovir (AIC246)

Letermovir inhibits the viral terminase, has good oral bioavailability and is well tolerated. Letermovir performed well in the context of pre-emptive treatment of CMV following kidney transplantation [11], and as primary CMV prophylaxis in HSCT recipients [12]. A phase III trial in HSCT is in recruitment (http://clinicaltrials.gov NCT02137772).

5.3. Intravenous immunoglobulin

Either standard human immunoglobulin or CMV hyperimmune globulin may be used to treat or prevent CMV complications in pregnancy or transplantation. However, evidence for effectiveness is questionable [13].

5.4. Artesunate

Artesunate is an anti-malarial drug which inhibits CMV replication in *vitro* and *vivo* [14]. Publications on the use of Artesunate as CMV treatment are limited to thirteen transplantation patients and show variable efficacy [15,16], and favourable outcomes may be limited to mild disease [17].