Cytovir CMV for cytomegalovirus infection in patients undergoing allogeneic haematopoietic stem cell transplantation

LAY SUMMARY

Cytomegalovirus (CMV) is a common viral infection which is carried by around 50% of the population and causes no harm to healthy people. However, for people undergoing blood or bone marrow transplantation it can cause serious complications due to their reduced immunity to infection.

Cytovir CMV is a new treatment that aims to prevent and treat CMV infection following blood or marrow transplantation. It is made up of immune cells that specifically attack CMV and it is administered by intravenous infusion.

Cytovir CMV is currently being studied to see how well it works and whether it is safe to use in people who have undergone blood or marrow transplantation. It is already available to specialist transplant centres in the UK.

NIHR HSRIC ID: 11473 and 6243
TARGET GROUP

- Prevention and treatment of cytomegalovirus (CMV) infection following allogeneic haematopoietic stem cell transplantation (HSCT) from a sibling or unrelated donor.

TECHNOLOGY

DESCRIPTION

Cytovir CMV (CMV-specific T cell therapy; immunoprophylactic adoptive cell therapy) is a CMV-specific T cell-based therapy. CMV-specific memory T cells can be directly selected from a CMV seropositive donor and infused into the patient to reconstitute immediate and long-lasting immunity against CMV infection. In clinical trials, Cytovir CMV was administered via intravenous (IV) infusion at a dose of up to $5 \times 10^4$ CD3+ T cells/kg.

Cytovir CMV is a cellular therapy product as defined by the EU Tissue and Cells Directive and does not fall under the definition of a medicinal product.

INNOVATION and/or ADVANTAGES

Cytovir CMV can be placed on the market in the UK with the appropriate manufacturing license and provides an additional treatment option for this patient group.

DEVELOPER

Cell Medica Ltd.

AVAILABILITY, LAUNCH OR MARKETING

The company report that Cytovir CMV has been classified as cellular therapy by the MHRA and is available to specialist transplant centres in the UK upon request.

PATIENT GROUP

BACKGROUND

CMV is a common virus that spreads via contact with body fluids. It is one of the herpes group of viruses, where primary infection is followed by life-long latency, and an estimated 50-80% of adults are infected with CMV in the UK. Most healthy people with acquired CMV infection will generally have few, if any, symptoms. However, CMV is a frequent complication in immunocompromised patients with impaired cellular immunity and is a major cause of morbidity and mortality following HSCT. If left untreated, CMV infection can progress to CMV disease, most commonly affecting the lungs, gastrointestinal tract, eyes, liver or central nervous system. In addition to the direct effects of CMV infection, tissue invasive CMV disease may be associated with increased risk of graft versus host disease, myelosuppression, and invasive bacterial and fungal infections.
This topic is relevant to:

HSCT, also known as blood and marrow transplantation (BMT) is used to treat a range of haematological and, increasingly, non-haematological disorders. CMV infection and subsequent CMV disease occur frequently in allogeneic (donor) HSCT recipients due to the severe and prolonged cellular immunodeficiency seen in these patients. It is reported that up to 50% of CMV seropositive recipients of allogeneic HSCT experience CMV reactivation, regardless of the donor's serostatus. CMV seronegative patients receiving donations from CMV seropositive individuals develop primary CMV infection in 30% of cases and have an increased mortality despite being managed post-transplant with leukodepleted or CMV seronegative blood products.

In 2013, 1,602 patients underwent allogeneic haematopoietic stem cell transplantation in the UK. The population likely to be eligible to receive Cytovir CMV could not be established from available routinely published sources.

RELEVANT GUIDANCE

NICE Guidance
- None identified.

Other Guidance
- British Committee for Standards in Haematology, the British Society of Blood and Marrow Transplantation and the UK Virology Network. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. 2013.
CURRENT TREATMENT OPTIONS

Where possible, donor and recipient CMV status should be established before any transplant procedure, and CMV status should be matched\(^4\). Seropositive patients having CMV seropositive donors have been shown to have better survival than seropositive patients receiving donations from CMV seronegative individuals\(^{11}\). Donors or recipients who are initially found to be CMV seronegative should be retested pre-transplant to exclude primary CMV infection and apparent CMV seroconversion in potential transplant recipients who have received unscreened blood products should be actively investigated to exclude passive acquisition of antibody.

Prophylactic and pre-emptive antiviral strategies can reduce CMV incidence, and monitoring of CMV levels in the blood is essential in either strategy\(^4\). Monitoring of CMV should be undertaken at least weekly for the first 3 months post-HSCT\(^4\).

Current antiviral agents recommended for the prevention and treatment of CMV post HSCT (though not specifically licensed for this indication) include\(^4\):

- Primary prophylaxis with acyclovir or valaciclovir.
- Secondary prophylaxis with valaciclovir or valganciclovir.
- Ganciclovir is recommended as first line pre-emptive therapy, with valganciclovir and foscarnet recommended as alternatives.
- Cidofovir may be considered as third line therapy in patients unresponsive or intolerant to ganciclovir or foscarnet.

Any CMV seronegative HSCT recipient transplanted from a CMV seronegative donor who develops CMV infection post-transplant must be reported to the Serious Hazards of Transfusion (SHOT) scheme\(^4\).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMPACT, NCT01077908, ISRCTN74928896; Cytovir with best available antiviral drug therapy (BAADT) vs BAADT; phase III.</th>
<th>ASPECT, NCT01220895, ISRCTN53325562, Cytovir with BAADT vs BAADT; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Cell Medica Ltd.</td>
<td>Cell Medica Ltd.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
<td>Complete and published in abstract.</td>
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<tr>
<td>Source of information</td>
<td>Publication(^1,3), trial registry(^15).</td>
<td>Abstract(^2,3), trial registry(^16).</td>
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<tr>
<td>Location</td>
<td>UK.</td>
<td>UK.</td>
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<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=91; aged ≥18 years; CMV seropositive allogeneic T cell depleted (alemtuzumab containing conditioning regimen) HSCT recipient with CMV seropositive sibling donor; donor engraftment (neutrophils &gt;0.5x10(^9)/l).</td>
<td>n=51; aged ≥16 years; CMV seropositive allogeneic T cell depleted (alemtuzumab-containing conditioning regimen) HSCT recipient with CMV seropositive unrelated donor; donor engraftment (neutrophils &gt;0.5x10(^9)/l).</td>
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<td>Schedule</td>
<td>Randomised to Cytovir CMV, single infusion (up to 100ml) containing a maximum of 5x10(^8) CD3(^+) T cells/kg at 27 days post-HSCT in combination with BAADT, ganciclovir, IV, 5mg/kg twice daily, valganciclovir, oral, 900mg twice daily, foscarnet, IV, 90mg/kg twice daily; or BAADT alone (regimens described Following single positive CMV PCR result, randomised to Cytovir CMV, single infusion (up to 100ml) containing a maximum of 3x10(^8) CD3(^+) T cells/kg, in combination with BAADT, ganciclovir, IV, 5mg/kg twice daily, valganciclovir, oral, 900mg twice daily, foscarnet, IV, 90mg/kg twice daily; or BAADT alone (regimens</td>
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<th>Follow-up</th>
<th>6 months follow-up.</th>
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<td>Primary outcome/s</td>
<td>Secondary CMV reactivations.</td>
<td>CMV specific immune reconstitution.</td>
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<td>Secondary outcome/s</td>
<td>No quality of life measures included in trial outcomes.</td>
<td>EQ-5D&lt;sup&gt;a&lt;/sup&gt;; EQ-5D VAS&lt;sup&gt;b&lt;/sup&gt;.</td>
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<td>Key results</td>
<td>Preliminary analysis for Cytovir CMV and control arm respectively: CMV reactivations, 0.75 vs 1.0/patient; patients experiencing &gt;1 treatment episode (%), 15 vs 26; new onset GvHD (%), 6.7 vs 3.2; mean duration of CMV treatment days, 19.1 vs 27.3 (p=0.14).</td>
<td>Interim analysis for Cytovir CMV and control arm respectively: new onset GvHD&lt;sup&gt;c&lt;/sup&gt; (%), 17.6 vs 27.3; fold change from baseline (peak) in CMV specific cells (mean ±SEM), 109.1 ± 42.5 vs 10.5 ± 7.1 (p=0.017); absolute change from baseline (peak) in CMV specific cells/ml (mean ± SEM), 20870 ± 6766 vs 4867 ± 2533 (p=0.056).</td>
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<td>Adverse effects (AEs)</td>
<td>For Cytovir CMV and control arm respectively: participants with ≥1 serious AE (%), 40.0 vs 32.3.</td>
<td>No evidence of increased incidence of new onset acute GvHD with Cytovir CMV treatment, and no other safety signals related to Cytovir CMV infusion were detected.</td>
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**ESTIMATED COST and IMPACT**

**COST**

Cytovir CMV is commercially available in the UK for £20,000.

**IMPACT - SPECULATIVE**

- **Impact on Patients and Carers**
  - Reduced mortality/increased length of survival
  - Other:
  - Reduced symptoms or disability
  - No impact identified

- **Impact on Health and Social Care Services**
  - Increased use of existing services
  - Re-organisation of existing services
  - Other:
  - Decreased use of existing services
  - Need for new services
  - None identified

- **Impact on Costs and Other Resource Use**
  - Increased drug treatment costs
  - Other increase in costs:
  - Other:
  - Reduced drug treatment costs
  - Other reduction in costs:
  - None identified

- **Other Issues**
  - <sup>a</sup> EuroQol, a standardised quality of life measure.
  - <sup>b</sup> EuroQol, patient-reported quality of life measure.
  - <sup>c</sup> Graft-versus-host disease.
Clinical uncertainty or other research question identified: None identified

REFERENCES

10 George B, Pati N, Gilroy N et al. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivations after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. Transplant Infectious Disease 2010;12:322-329.