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Horizon Scanning Research & Intelligence Centre

Letermovir for the prevention of cytomegalovirus infection in sero-positive patients undergoing allogeneic haematopoietic stem cell transplantation

LAY SUMMARY

Cytomegalovirus is a common virus and most people become infected in childhood. The virus is spread through bodily fluids, such as saliva or urine, and can easily be spread by close contact with children, such as when changing nappies. Once someone becomes infected, the cytomegalovirus will stay in their body for the rest of their lives without causing problems. Most people do not have symptoms and will not need treatment. However, people with weakened immune systems need to be treated to avoid complications.

Letermovir is a new drug that is taken by mouth as a tablet to prevent cytomegalovirus infection. Some studies have suggested that this drug can help prevent infection in people undergoing allogeneic stem cell transplantation (sometimes called a bone marrow transplant), and if letermovir is licensed for use in the UK, it could be a new treatment option for people undergoing this procedure.

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NHS National Institute for Health Research

TARGET GROUP

- Prevention of cytomegalovirus infection in sero-positive adult patients undergoing allogeneic haematopoietic stem cell transplantation.

TECHNOLOGY

DESCRIPTION

Letermovir (AIC 001; AIC 090027; AIC 246; BAY 73-6327; MK 8228) is a novel viral terminase inhibitor, which prevents proper DNA cleavage into unit-length genomes, thus inhibiting the release of infectious viral particles. Letermovir is intended for the prevention of cytomegalovirus (CMV) infection in sero-positive adult patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT). In a phase III clinical trial, letermovir is administered at 240mg orally once daily for participants receiving ciclosporin A, and 480mg orally once daily for those not receiving ciclosporin A[1]. For patients not able to swallow or otherwise absorb the drug from the gastrointestinal tract, letermovir will be administered via intravenous (IV) infusion. Letermovir is administered for 14 weeks after transplantation[1].

Letermovir does not currently have a Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, letermovir will offer an additional treatment option for this patient group.

DEVELOPER

Merck Sharp & Dohme Ltd (MSD).

AVAILABILITY, LAUNCH OR MARKETING

Letermovir is a designated orphan drug in the EU and USA. It is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

CMV is a common virus that belongs to the herpes family[2]. An estimated 50-80% of adults in the UK are sero-positive for CMV, indicating past infection[2]. Once infected, the virus persists in the body in an inactive or latent state[3]. It can become re-activated if an individual's immune system is compromised, such as in those taking immunosuppressant medication as part of a HSCT regimen[2,3]. CMV is transmitted through bodily fluids such as saliva and urine. Most cases are asymptomatic, though symptoms in immunocompetent individuals can include mild flu like symptoms, such as high temperature, sore throat and painful lymphadenopathy[2,3]. However, in immunocompromised individuals, CMV infection can result in more serious infection, including a serious overwhelming infection with multi-organ involvement. If left untreated, CMV infection can progress to CMV disease, most commonly affecting the lungs, gastrointestinal tract, eyes, liver or central nervous system[4]. 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[5].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- NHS England. 2013/14 NHS Standard Contract for haematopoietic stem cell transplantation (Adult). B04/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (All ages): revised. NHSCB/B04/P/a. January 2015.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (All ages). NHSCB/B04/P/a. April 2013.

CLINICAL NEED and BURDEN OF DISEASE

HSCT, also known as blood and marrow transplantation (BMT), is used to treat a range of haematological and, increasingly, non-haematological disorders[6]. In 2014, there were 1,346 non-paediatric allogeneic HSCT procedures performed in the UK[7].

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[8]. 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[9].

In 2014-15, there were 799 hospital admissions for CMV (ICD-10 B25.9) in England, resulting in 5,444 bed days and 980 finished consultant episodes[10].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- None identified.

Other Guidance

- American Society for Blood and Marrow Transplantation. Hematopoietic stem cell transplantation for multiple myeloma: guidelines from the American Society for Blood and Marrow Transplantation. 2015[11].
- NHS Commissioning Board. Clinical commissioning policy: haematopoietic stem cell transplantation. 2013[6].
- 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[4].
- British Society for Histocompatibility and Immunogenetics. Guidelines for selection and HLA matching of related, adult unrelated donors and umbilical cord units for haematopoietic progenitor cell transplantation. 2012/13[9].

- American Society for Blood and Marrow Transplantation. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. 2009[12].

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[8]. Donors or recipients who are initially found to be CMV seronegative should be retested pre-transplant to exclude primary CMV infection[4]. Apparent CMV seroconversion in potential transplant recipients who have received unscreened blood products should be actively investigated to exclude passive acquisition of antibody[4].

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 aciclovir 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

Trial	MK-8228-001, NCT02137772, 8228-001, 2013-003831-31, 152923; letermovir vs placebo; phase III.	NCT01063829, AIC246-01-II-02; letermovir vs placebo; phase II.
Sponsor	MSD.	AiCuris.
Status	Ongoing.	Published.
Source of information	Trial registry[1].	Publication[13], trial registry[14].
Location	EU (incl UK) and USA.	USA and Germany.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n=540 (planned); aged ≥18 years; CMV sero-positive, documented within 1 yr before HSCT; no previous allogeneic HSCT; no history of end-organ disease 6 mths before randomisation; no evidence of CMV viraemia; not received the following within 7 days before screening and no plans to receive during the study: ganciclovir, valganciclovir, foscarnet, aciclovir, valaciclovir, or famciclovir; not received the following within 30 days	n=131; aged ≥18 years; CMV sero-positive before transplantation; first allogeneic human blood precursor cell (HBPC) transplantation performed for leukaemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, or myelodysplastic and myeloproliferative disorders; evidence of post transplantation engraftment; no previous anti-CMV therapy after the allogeneic HBPC transplantation; no

	before screening and no plan to receive during the study: cidofovir, CMV hyper-immune globulin, any investigational CMV antiviral agent or biological therapy; no human immunodeficiency virus (HIV) antibody, hepatitis C virus (HCV) antibody with detectable HCV ribonucleic acid, or hepatitis B surface antigen (HBsAg) within 90 days before randomisation.	mismatched or cord blood transplant recipients; no current or history of end-organ CMV disease; no graft vs host disease.
Schedule	Randomised to receive letermovir or placebo, once daily for up to 14 weeks after transplantation. Letermovir is administered at 240mg orally once daily for participants receiving ciclosporin A, and 480mg orally once daily for those not receiving ciclosporin A. For patients not able to swallow or otherwise absorb the drug from the gastrointestinal tract, letermovir will be administered via IV infusion.	Randomised to letermovir 60mg, 120mg or 240mg, or placebo, all taken orally once daily for 12 wks after engraftment.
Follow-up	Active treatment for up to 14 wks, follow-up for up to 24 wks.	Active treatment for up to 12 wks, follow-up for up to 92 days.
Primary outcome/s	Percentage of participants with clinically-significant CMV infection.	CMV reactivation or human CMV end-organ disease.
Secondary outcome/s	Time to onset of clinically-significant CMV infection and initiation of pre-emptive therapy for CMV viraemia; percentage of participants with: clinically-significant CMV, CMV disease and pre-emptive therapy for CMV viremia; quality of life measured as exploratory outcomes using EuroQol five dimensions questionnaire (EQ-5D) and Functional Assessment of Cancer Therapy – bone marrow transplant (FACT-BMT).	Not stated.
Key results	-	For letermovir 60mg, 120mg and 240mg or placebo, respectively: prophylaxis failure, 48%, 32%, 29% and 64%. Time to onset of prophylaxis failure was statistically significantly longer with letermovir 240mg compared with placebo (p=0.002).
Adverse effects (AEs)	-	The safety profile of letermovir was reportedly similar to placebo, with no indication of haematological toxicity or nephrotoxicity. An AE was observed in 94% of the letermovir 60mg and 120mg groups, and 100% of the 240mg group; the majority were mild or moderate. 24% of pts receiving letermovir had a severe AE vs 30% in the placebo group. Most AEs were related to gastrointestinal disorders (66% in letermovir groups vs 61% in placebo) or infections (mainly CMV – 59% in the letermovir groups vs 76% in the placebo group). Discontinuation of the randomised therapy was 26% vs 58% in the letermovir vs placebo groups,

		respectively. Treatment related AEs considered to be drug related as judged by the site investigators were reported in 17% of participants in the letermovir groups vs 33% in the placebo group.
Expected reporting date	Study completion date reported as Jan 2017.	-

ESTIMATED COST and IMPACT

COST

The cost of letermovir is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other
- ☐ No impact identified

Impact on Health and Social Care Services

- ☐ Increased use of existing services
- ☑ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other
- ☐ None identified

Impact on Costs and Other Resource Use

- ☑ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs
- ☐ Other reduction in costs:
- ☐ Other
- ☐ None identified

Other Issues

- ☐ Clinical uncertainty or other research question identified
- ☑ None identified

REFERENCES

1 ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02137772 Accessed 22 March 2016.
2 NHS Choices. Cytomegalovirus (CMV). http://www.nhs.uk/conditions/cytomegalovirus/Pages/Introduction.aspx Accessed 22 March 2016.
3 CMV Action. Basics about CMV. http://cmvaction.org.uk/what-cmv/basics-about-cmv Accessed 22 March 2016.
4 Emery V, Zuckerman M, Jackson G *et al*. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. British Journal of Haematology 2013;162:25-39.
5 Ariza-Heredia EJ, Nesher L and Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini review. Cancer Letters 2014;342(1):1-8.

6 NHS Commissioning Board. Clinical commissioning policy: haematopoietic stem cell transplantation (all ages): revised. London: NHS England; January 2015. www.england.nhs.uk
7 British Society of Blood and Marrow Transplantation. 2014 Activity. http://bsbmt.org/2014-activity/ Accessed 22 March 2016.
8 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.
9 British Society for Histocompatibility and Immunogenetics. Guidelines for selection and HLA matching of related, adult unrelated donors and umbilical cord units for haematopoietic progenitor cell transplantation. www.bshi.org.uk/assets/pdf/HSCTGuide.pdf Accessed 22 March 2016.
10 Health & Social Care Information Centre. Hospital episode statistics for England. Admitted Patient Care statistics, 2014-15. www.hscic.gov.uk
11 Shah N, Callander N, Ganguly S *et al*. Hematopoietic stem cell transplantation for multiple myeloma: guidelines from the American Society for Blood and Marrow Transplantation. Biology of Blood and Marrow Transplantation 2015;21(7):1155-1166.
12 Tomblyn M, chiller T, Einsele H *et al*. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biology of Blood and Marrow Transplantation 2009;15:1143-1238.
13 Chemaly RF, Ullmann AJ, Stoelben S *et al*. Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation. New England Journal of Medicine 2014;370:1781-1789
14 ClinicalTrials.gov. Safety and efficacy study of a new antiviral drug to prevent cytomegalovirus reactivation in bone marrow transplanted patients. https://clinicaltrials.gov/ct2/show/NCT01063829 Accessed 22 March 2016.