KAROLINSKA
UNIVERSITY HOSPITAL

Immunosuppression after renal transplantation in children with increased immunological risk (<40 kg)
Prevention and treatment of CMV in connection with organ transplantation (LTX, NTX, NPTX, HTX)

CMV prophylaxis after transplantation (preferably started within 10 days after tx)

Given at:	Adults	Children
CMV-mismatch (D+/R-)	T Valcyte 900 mg x 1 3 months.*	M/T Valcyte x1 The dose is calculated according to: 7 x body surface (m^2) x GFR. This gives the dose in mg given 1 time/day. Maximum dose of 900 mg x1
ATG **(ex HTX, NPTX, Rejection Treatment)**	T Valcyte 900 mg x 1 3 months.*	M/T Valcyte x1 The dose is calculated as above
Repeated rejection treatment	Consider T Valcyte 900 mg x1 > 3 months.*	M/T Valcyte x1 The dose is calculated as above
Pronounced immunosuppression	Consider T Valcyte 900 mg x1 > 3 months.*	M/T Valcyte x1 The dose is calculated as above

*Dose according to renal function (e.g. cystatin-C GFR, see FASS).

Concentration determination: see below

Planning of the CMV prophylaxis should be clearly demonstrated by the epic crisis

CMV monitoring after transplantation

If prophylaxis are indicated, but cannot be given for any reason, the patient should be monitored with CMV DNA in blood every two weeks for 3 months. In all patients with mismatch ((D+/R-) the cover of positive CMV-DNA in blood should always be treated "preemptive". Reactivation in heavy immunosuppressed (ATG, repeated rejection) should most often be treated, see below.

In the case of monitoring (without prophylaxis) of D+/R, cover to positive CMV-PCR should always be treated "pre-emptive".

CMV treatment

	Adults	Children
Treatment dose	Cymevene 5 mg/kg x2 iv or T Valcyte 900 mg x2*	M/T Valcyte x2 The dose is calculated according to: 7 x body surface (m^2) x GFR. This gives the dose in mg to be given 2 times/day Maximum dose 900 mg x 2
Maintenance dose	Cymevene 5 mg/kg x1 iv (alt 6 mg/kg x 1 IV 5 dgr/v) or T Valcyte 900 mg x1*	M/T Valcyte x1 The dose is calculated according to: 7 x body surface (m^2) x GFR. This gives the dose in mg to be given 1 time/day Maximum dose 900 mg x 1

***** Dosing according to renal function (e.g. cystatin-C GFR, see FASS).

Concentration determinations need only be made in case of renal failure, suspected side effect or treatment failure. Even at dosing in young children, concentration measurements may be of value. The frequency of concentration determinations may be determined individually and preferably discussed with an infection consultant

Valcyte can most often be used but Cymevene is recommended for young children, severely ill patients, in case of poor intestinal function or severe renal failure, as the preparation is easier to adapt to the dose. As paediatric data on Valcyte are still limited, it is suggested to initially use Cymevene in young children and then switch to Valcyte when the patient is clinically improved.

Primary infection early after transplantation should always be treated even if asymptomatic and regardless of virus levels according to PCR. Symptomatic CMV infection and CMV infection with organ involvement should always be treated.

Reactivation with low virus levels (<5000 copies/ml) and without symptoms is common and rarely needs to be treated but new CMV-PCR should be checked after about 1 week.
In case of asymptomatic reactivation with high (> 5000 copies/ml) and/or rapidly rising virus levels, individual assessment is made, please consult with an infection consultant. Regardless of virus levels, the patient's immune status should always be taken into account in the pre-emptive treatment of symptom-free patients. Repeated rejection therapy and ATG strengthen the indication. In case of uncertainty about symptoms and/or organ involvement caused by CMV, it is important to continue the diagnosis as described above.

Treatment duration**at least 2 weeks**. Treatment continues until the patient is symptom-free and preferably also has clearly decreasing viral levels. Subsequent maintenance dose treatment may be considered, as a rule in 1-3v. CMV-PCR in blood is taken at the start of treatment and then 1ggr/v.

If there is no clinical response or persistently high viral levels, consider ganciclovir resistance. However, it may take up to a couple of weeks before the blood virus level decreases, even in the case of effective treatment with clinical response. In case of suspicion of ganciclovir resistance consultation with infection consultant.

General background

Primary infection usually occurs in young children, after which viruses remain latent in various immunological cells, including macrophages and monocytes. Mild reactivation of the infection without symptoms is also common in immune health. After organ transplantation, there is a risk of symptomatic reactivation or primary infection (CMV disease) that can be severely erupting. The risk depends on the degree of immunosuppression and the outcome of CMV serology in the recipient and donor.

If the recipient is CMV IgG negative and receives organs from donor that is CMV IgG positive (CMV recipient-negative/donor-positive, R-/D+, also called CMV mismatch) there is a very high probability of CMV disease. The risk of serious infection is significantly greater, especially if it occurs early after the transplant. Recipients that are CMV IgG positive (R+) have lower risk, and for CMV IgG negative recipients receiving organs from CMV IgG negative donors (R-/D-) the risk is very small. Pronounced immunosuppression increases the risk of serious infection, both primary and reactivation. ATG results in particular increased risk due to a pronounced impact on T-cell defence.

Symptoms

- Asymptomatic, common in reactivation and in primary infection late after transplantation.

- CMV syndrome: fever, leukopenia and/or thrombocytopenia, low CRP. Common

- Invasive CMV disease with organ involvement:
  CMV can affect all organs, but most common is gastritis/enteritis/colitis
  There is also an increased risk of invasive infection in the transplanted organ, for example.
- Hepatitis, in liver transplantation
- Pneumonitis, in lung transplantation
- Nephritis in kidney transplantation

Very unusual: encephalitis, retinitis

Diagnostics

Serology CMV IgG is taken prior to transplantation on both recipient and donor. If CMV IgG is positive, the patient has a completed, latent infection. If low antibody levels/limit values may be discussed during daytime with the microbiologist/VirusLab. An alternative explanation of low

Print date: 2022-05-27

antibody levels are passively transmitted antibodies (maternal, blood products). After transplantation, serology is not reliable to detect active infection.

In case of suspected CMV disease/disorder after transplantation, CMV-PCR (i.e. quantitative CMV DNA in blood) is taken.

In case of signs of organ involvement, take samples, if possible, from the respective premises:

—Hepatitis: liver biopsy for PAD and immunohistochemistry. Do not take PCR on biopsy material as it is too sensitive and not diagnostic for local infection.
- Gastritis/enteritis/colitis: endoscopy with biopsy for PAD and immunohistochemistry. Do not take PCR as above.
- Nephritis: renal biopsy for PAD and immunohistochemistry. Do not take PCR as above.
—Pneumonitis: CMV-PCR in blood + typical radiological image. Any cytology of BAL (morphology + immunhistochemistry), insensitive. However, PCR on BAL fluid very sensitive and nonspecific, negative PCR excludes CMV pneumonitis. Currently, quantitative PCR evaluation is ongoing on BALfluid.
—Encephalitis: LP with wide sampling including CMV-PCR in liquor (discussion infection consultant)

This PM has been produced by:

Infection
Lisa Swartling, Chief Physician
Elda Sparrelid, Chief Physician

Transplantation
Greg Nowak, Senior Physician and Associate Professor
Lars Wennberg, Senior Physician and Associate Professor
Bo-Göran Eriksson, Senior Physician and Professor
Angelica Strand, doctor

Paediatric medicine
Björn Fischler, Chief Physician
Rafael Krmar, Chief Physician

Cardiologist
Inger Hagerman, Chief Physician

References:

1) Pharmacological treatment of cytomegalovirus infections — updated recommendation,

Organisation:

The Medical Products Agency 2010
2) British Transplantation Society Guidelines for the prevention and management of CMV disease after solid organ transplantation, Aug 2011.

Version history

Each document should contain a history that tells you, for each version, what changed, who made the change and when the change was made.

Version	Date	Change and comment	Responsible
3	2018-11-16	New template, new organisation.	Lars Wennberg
2	2014-02-24	The document recast by Lars Wennberg; applies to all organ-transplanted patients	Lars Wennberg/Tarja Tervonen
1	2012-10-13	The document was copied to Domino LIS without changing the content.	Tarja Tervonen

Determiner: Lars Wennberg/Carolinska/SLL
Organisation: