Cytomegalovirus infection after transplantation: prevention is still the challenge

Citomegalovirus pós-transplante: o desafio ainda é a prevenção

Authors
José Otto Reusing Junior [1]
Elias David-Neto [1]

[1] Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo - SP, Brazil.

Despite recent advances in cytomegalovirus (CMV) diagnosis and treatment, it is still the main viral infectious agent after transplantation. Without prevention and under current standard immunosuppression, which includes tacrolimus and mycophenolate, the incidence of CMV disease ranges from 17-67%.[1,2] Therefore CMV prevention is necessary but demands high health care resources, either as universal prophylaxis or preemptive therapy.

In this issue, Felipe CR *et al*. brought us a welcomed study about CMV with the biggest Brazilian cohort of patients so far.[3] It informs about recent impact of CMV on kidney transplantation. The small proportion of IgG seronegative patients (6%) corroborates that in Brazil the main issue is the recipient of intermediate risk (seropositive).

This study shows that CMV infection motivated immunosuppression changes in 63% of cases (*vs*. 31% in the no-CMV group). Fortunately most cases of disease were mild and presented either as viral syndrome or with gastrointestinal symptoms (possible invasive disease). No death was attributed to CMV. However it was associated with more subsequent acute rejection episodes and lower graft function one year post-transplant. Even though a graft-survival difference was not found, the follow-up time was only 12 months, probably too short to definitively exclude this effect.

In addition to recipient negative serology, other known risk factors[4] were associated with CMV in this cohort: the use of mycophenolic acid formulations, anti-thymocyte globulin (ATG), low estimated glomerular filtration rate and recipient age. Accordingly to their findings, low graft function has emerged as a risk factor for CMV in some studies.[2,4]

One feature deserves special attention: the high incidence (17%) of CMV disease in the present data, most of them early and still during viral monitoring. This is the same incidence from another Brazilian cohort, which however did not implement any CMV prevention.[1] It is not clear if the low efficacy of the preventive strategy from Felipe *et al*.[3] was in part due to logistic problems, antigenemia sensitivity or the threshold for treatment.[1] But it seems that the biweekly monitoring was not enough to avoid CMV disease in patients given ATG. The Updated International Consensus Guidelines recommend that monitoring for preemptive therapy should be on a weekly basis.[5]

mTOR (mammalian target of rapamycin) inhibitors are known for their protective role against CMV and some viruses after transplant, as shown previously by the same group.[6] But it remains to be proven whether their combination with low-dose calcineurin inhibitor is safe enough to become the standard immunosuppression for kidney transplantation.

In Brazil, a 3-month prophylaxis with valganciclovir costs between 1,880 and 7,515 US dollars[a]. It is 3.2-7.1 times the cost of monitoring with preemptive therapy, depending on renal clearance and test frequency. Because of the high cost of universal prophylaxis, the path to reduce CMV burden lies in a targeted prevention.

Submitted on: 09/27/2017.
Approved on: 10/03/2017.

Correspondence to:
José Otto Reusing Junior.
E-mail: jose.otto@hc.fm.usp.br

DOI: 10.5935/0101-2800.20170064

A targeted strategy should be cost-effective and expose less patients to the anti-CMV drugs' myelotoxicity. Along with the clinical variables demonstrated here, CMV-specific T-cell immunity tests might have a role in this risk stratification.[5]

Even in a high-volume transplant center with consolidated health care and logistics, CMV prevention proves not to be optimal. For maintenance immunosuppression without mTOR inhibitor, a new risk stratification strategy is necessary. We expect that, in the future, a predictive score with these and other variables could be developed and tested to tailor prevention in higher risk subgroups.

References

1. David-Neto E, Triboni AH, Paula FJ, Vilas Boas LS, Machado CM, Agena F, et al. A Double-Blinded, Prospective Study to Define Antigenemia and Quantitative Real-Time Polymerase Chain Reaction Cutoffs to Start Preemptive Therapy in Low-Risk, Seropositive, Renal Transplanted Recipients. Transplantation. 2014. PMID: 24839894 DOI: http://dx.doi.org/10.1097/TP.0000000000000189
2. De Keyzer K, Van Laecke S, Peeters P, Vanholder R. Human cytomegalovirus and kidney transplantation: a clinician's update. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2011;58(1):118-26. DOI: http://dx.doi.org/10.1053/j.ajkd.2011.04.010
3. Felipe C, Ferreira AN, Bessa A, et al. The current burden of cytomegalovirus infection in kidney transplant recipients receiving no pharmacological prophylaxis. J Bras Nefrol. 2017;39(4):413-423.
4. San Juan R, Aguado JM, Lumbreras C, Fortun J, Munoz P, Gavalda J, et al. Impact of current transplantation management on the development of cytomegalovirus disease after renal transplantation. Clin Infect Dis. 2008;47(7):875-82. DOI: http://dx.doi.org/10.1086/591532
5. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96(4):333-60. PMID: 23896556 DOI: http://dx.doi.org/10.1097/TP.0b013e31829df29d
6. Tedesco-Silva H, Felipe C, Ferreira A, Cristelli M, Oliveira N, Sandes-Freitas T, et al. Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses. Am J Transplant. 2015;15(10):2655-64. DOI: http://dx.doi.org/10.1111/ajt.13327

[a] Antiviral prices from ANVISA site (www.portal.anvisa.gov.br), as maximal trade-value to government, São Paulo State. Antigenemia (pp65) price from Virology Laboratory from Instituto de Medicina Tropical de São Paulo. Expenses with logistics, nursing and adverse events were not considered.