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Torque teno virus monitoring in transplantation: The quest for standardization

To the Editor:

We read with interest the recent article by Fernandez-Ruiz et al detailing the power of early Torquetenovirus (TTV) monitoring after kidney transplantation at predicting events associated with excessive immune suppression (opportunistic infections and secondary cancers).[1]

Despite transplantation of commensal flora possibly complicating kinetics interpretation,[2] TTV is emerging as a promising marker to assess global functional immune competence, to predict post-transplant immune-related adverse events, and eventually to customize immunosuppression. Table 1 summarizes what is currently known about TTV predictive cutoffs from the many single-center studies run to date in different transplantation settings (studies reporting only correlation analyses or only differences between medians/means were excluded).

Although some interlaboratory variability is expected and differences in transplant type and (induction and maintenance) immunosuppressive regimens among centers could account for most of the observed cutoff differences, we are still lacking multicenter prospective trials with fixed time points from various organs and Hematopoietic stem cell transplantation (HSCT) assessing the power of early TTV viremia monitoring at predicting immune-related adverse events. Two tools should facilitate the setup of such trials. One is the availability of standardized commercial assays,[3] and the other is the availability of TTV-specific independent external quality assessment (EQA) pilot programs like that recently run by Quality Control for Molecular Diagnostics (QCMD).[4] Additionally, welcomed measures would be standardization of cutoff reporting units (Area under the curve copies × days/mL vs log copies/mL vs fold change) and identification of the best time points to measure TTV viremia in order to get predictions. The earlier the time point, the most useful it is for treating clinicians and patients. Earliest time points additionally remove the biases associated with different plasma levels of maintenance immunosuppressants and potentially provide cutoffs irrespective of transplant subtype.

Certainly, many time points stemming from retrospective studies are often either clinically useless (such as "days before a clinical event") or imply high sampling frequencies and costs (such as wide time points defined as "monitoring windows").

After the aforementioned standardizations are successfully deployed in prospective trials, TTV would be able to join the current list of predictive biomarkers in transplantation[5] and eventually become the most useful orphan virus to date.

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Keywords

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TABLE 1 List of papers in which receiver operating characteristic curve analysis for TTV viremia was calculated for predicting posttransplant immune-related adverse events

Transplant	Study	No. examined	Follow-up (days)	Endpoint monitored	TTV DNA cutoff[a]	Time point of prediction (days)	Sensitivity-specificity	Reference
HSCT	Retrospective	44	120	High-level CMV DNA	≤2.8[b]	20–30	64%-70%	Albert et al.[6]
		23	200	Viral infections and/or GVHD	8.5	30	NR	Gilles et al.[7]
Kidney	Retrospective	34	365	Biopsy-proven rejection	10-fold decrease	30 d prerejection	74%–99%	Frye et al.[8]
	Prospective	221	365	Microbial infections	>3.1	30	90%–31%	Fernandez-Ruiz et al[1]
				Cancer	>4.6	30	76%–66%	
		124	269	Microbial infections	>9.5	> 92	90%–20%	Strassl et al.[9]
Kidney/liver	Retrospective	235	360	CMV infection	>3.4	0–10	83%–56%	Maggi et al.[10]
Liver	Retrospective	39	360	ACGR	<1.4	0	NR	Simonetta et al.[11]
		63	360	CMV infection	>7.5	0–30	80%–84%	Ruiz et al.[12]
				Moderate ACGR	<4.7		100%–77%	
Lung	Retrospective	31	720	Microbial infections	>9.3	150–720	54%–91%	Gorzer et al.[13]
	Prospective	143	197-1612	Microbial infections	>9.2	90 days monitoring window	87–71%	Jaksch et al.[14]
				CLAD	<8.0		95%–55%	
	Case control	29	1095	CLAD	<7.0	50 days pre-CLAD	64%–87%	Gorzer et al.[15]
Lung/heart	Retrospective	96	495	Graft rejection	NR	NR	NR	De Vlaminck et al.[16]

ACGR, acute cellular graft rejection; CLAD, Chronic lung allograft dysfunction; CMV, Cytomegalovirus; GVHD, graft vs host disease; HSCT, Hematopoietic stem cell transplantation; NR, not reported.
[a]Log copies/mL. TTV DNA quantification was performed by the in-house real-time polymerase chain reaction developed by Maggi et al.[17] Exceptions were Simonetta et al [11] (in house-real-time PCR by Moen et al[18]), Fernandez-Ruiz et al[1] (commercial assay by BioMerieux), and De Vlaminck et al[16] (by GRAMMy algorithm).
[b]Area under the curve (AUC) for log copies × days × mL^{-1}.