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MATCH
Management of Post-Transplant Infections in Collaborating Hospitals

Cytomegalovirus And Drugs Used To Prevent And Treat This Infection As Risk Factors For Longer Term Deterioration Of Kidney Function After Solid Organ And Human Stem Cell Transplantation

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BACKGROUND

- Deterioration of kidney function is a serious complication following transplantation
- Factors associated with longer-term deteriorating kidney function after transplantation are poorly understood

Hypothesis

- The occurrence of post-transplant Cytomegalovirus (CMV) infection may increase deterioration; directly by causing nephritis or secondarily by the use of nephrotoxic antiviral drugs

Objectives

- To assess effects of CMV infection, CMV viral load and drugs used as prophylaxis or treatment on evolution of eGFR in the first year following a transplantation

METHODS

Patients and study design

- Inclusion: Consecutive transplanted patients (2004 to 2008), monitored for CMV infection, above 18 years at the time of their transplantation
- Estimated glomerular filtration rate (eGFR/ml/min/1.73m²) was calculated using the four variable MDRD equation*.

  If more than one eGFR measurement recorded on any one day the average value for that day was used
- Three groups were established: (i) non-kidney solid organ transplant, (ii) kidney transplant, and (iii) human stem cell transplant (HSCT) recipients

Statistical methods

- Factors affecting eGFR levels from month 1 to 12 following the transplantation were evaluated by regression coefficients using unadjusted and adjusted multivariable mixed effects models. Models included both fixed time and time-dependent covariates

*Andrew S. Levey; Lesley A. Stevens; Christopher H. Schmid; et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5;150(9):604-12

Table 1

Characteristics of 303 patients 1 month after transplantation according to the type of transplantation

	Kidney transplant	Non kidney solid organ transplant*			HSCT	Total
	N=93	Heart N=8	Liver N=31	Lung N=94	N=77	N=303
Gender: N (%) Female: Male:	39 (41.9%) 54 (58.1%)	2 (25.0%) 6 (75.0%)	16 (51.6%) 153 (48.4%)	49 (52.1%) 45 (47.9%)	29 (37.7%) 48 (62.3%)	**135 (44.6%) 168 (55.5%)**
Age at transplantation (median years, IQR)	41 (32, 54)	50 (38, 56)	46 (40, 59)	52 (37, 58)	38 (25, 48)	**45 (32, 56)**
Year of transplantation (median years, IQR)	2007 (2006, 2007)	2007 (2005, 2007)	2006 (2005, 2007)	2006 (2005, 2007)	2005 (2004, 2006)	**2006 (2005, 2007)**
Prior transplantation (Y, %)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	3 (3.9%)	**5 (1.7%)**
eGFR at transplant (median mL/min/1.73 m2, IQR)	**7.7** (5.8, 11.4)	**84.2** (71.5, 111.0)	**70.6** (60.2, 124.4)	**121.7** (93.9, 142.0)	**97.9** (79.6, 132.8)	**80.7 (12.0, 124.8)**
eGFR at month 1 (median mL/min/1.73 m², IQR)	**52.5** (39.0, 67.6)	**62.4** (43.4, 69.3)	**76.0** (47.2, 125.9)	**81.4** (60.4, 109.7)	**80.9** (55.9, 100.3)	**67.7 (47.9, 95.9)**

* Non kidney solid organ (heart, liver, lung) recipients are combined as one group in subsequent figures and tables as the evolution of kidney function from month 1 to month 12 was comparable among these three subgroups.

Table 2

eGFR, median (IQR) at month 1, 6 and 12 following kidney, non kidney solid organ, or HSCT. And evolution of eGFR (ml/min/1.73m²) from month 1-12 – adjusted regression coefficient for two factors found to influence the evolution.

eGFR (ml/min/1.73m²) Median (IQR)				
Patients	Kidney transplant	Non kidney solid organ transplant	Human stem cell transplant	Overall
1 month post transplantation	**52.5** (39.0 to 67.6) [n=93]	**78.3** (57.3 to 112.8) [n=133]	**80.8** (55.9 to 100.3) [n=77]	**67.7** (47.9 to 95.5) [n=303]
6 months post transplantation	**46.6** (35.0 to 55.7) [n=93]	**65.4** (44.8 to 84.2) [n=125]	**78.3** (58.6 to 94.3) [n=70]	**56.6** (43.3 to 81.6) [n=288]
12 months post transplantation	**46.4** (34.4 to 59.4) [n=74]	**52.8** (42.0 to 73.1) [n=105]	**83.5** (64.0 to 101.9) [n=63]	**54.8** (40.3 to 81.1) [n=242]
Evolution of eGFR (ml/min/1.73m²) from month 1-12 – regression coefficient (95% CI)*				
Per 5 days of follow-up month 1-12	-0.23 (-0.26 to -0.19) p<0.0001 [n=93]	-0.68 (-0.78 to -0.59) p<0.0001 [n=133]	-0.05 (-0.11 to 0.01) p=0.10 [n=77]	-0.25 (-0.29 to -0.22) p<0.0001 [n=303]
Per 5 ml/in/1.73m² higher eGFR at BL	3.28 (2.81 to 3.75) p<0.0001 [n=93]	3.00 (2.58 to 3.42) p<0.0001 [n=133]	2.57 (1.83 to 3.32) p<0.0001 [n=77]	2.96 (2.66 to 3.25) p<0.0001 [n=303]

*: Findings from model adjusted for the following time fixed variables: age, gender, transplantation type, eGFR prior to transplantation, eGFR at baseline, delta eGFR from transplantation to baseline. The following time updated variables were also included in the model: time from transplantation, CMV infection, CMV viral load area under the curve, use of valganciclovir, ganciclovir, foscovir, methylprednisolone, ciclosporin, tacrolimus, sirolimus, mycophenolic acid and mycophenolate mofetil.

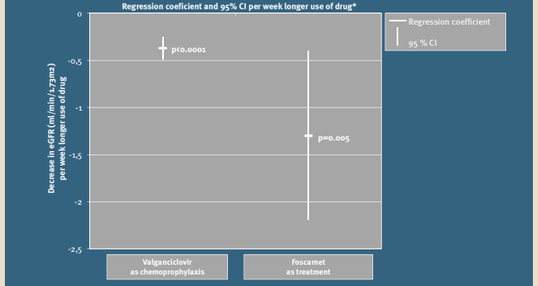
RESULTS

Tables and figures

- There were 303 individuals who satisfied the entry criteria
- Baseline characteristics for these patients are depicted in **Table 1**
- Overall eGFR decreased from a median (IQR) of 68 (48;96) at month 1 to 55 (40;81) at month 12 (**Table 2**)
- After adjustment, eGFR decreased by -0.23 [95% CI: -0,26 to -0.19, p<0.0001], -0.68 [95% CI -0.78 to -0.59, p<0.0001], and -0.05 [95% CI: -0.11 to 0.01, p=0.10] for each 5 days of follow up in kidney transplant, non kidney solid organ transplant, and HSCT recipients, respectively (**Table 2**)
- Valganciclovir used as CMV chemoprophylaxis was associated with a negative eGFR slope (-0.4 [-0.5 to -0.3] for each week longer usage, p<0.0001) (**Figure 1**)
- Use of foscarnet to treat CMV infection was associated with a negative eGFR slope (-1.3 [-2.2 to -0.4] ml/min/1.73m² for each week longer usage, p=0.005) (**Figure 1**)
- A total of 87 (29%) patients developed CMV infection during follow up
- Overall larger area under the curve CMV viraemia was associated with larger decline in eGFR (p=0.02) (**Figure 2**)

Figure 1

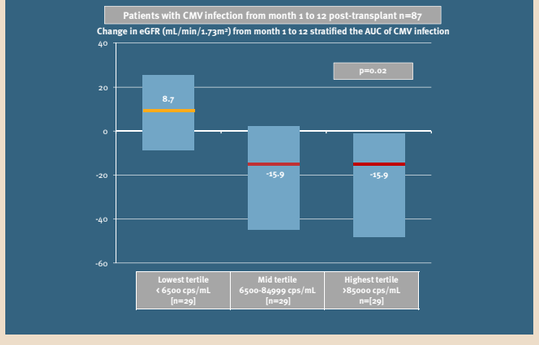
Effects of antiviral drugs used as prophylaxis and treatment for CMV



*: Findings from model adjusted for the following time fixed variables: age, gender, transplantation type, eGFR prior to transplantation, eGFR at baseline, delta eGFR from transplantation to baseline. The following time updated variables were also included in the model: time from transplantation, CMV infection, CMV viral load area under the curve, use of valganciclovir, ganciclovir, foscovir, methylprednisolone, ciclosporin, tacrolimus, sirolimus, mycophenolic acid and mycophenolate mofetil.

Figure 2

Effects of area-under-the-curve (AUC) CMV viral load on change in eGFR from month 1 to 12 after transplantation



CONCLUSION

- The eGFR decreased substantially in the first year among individuals undergoing kidney transplantation and, in particular, non kidney solid organ transplantation
- The eGFR remained stable in human stem cell transplant recipients
- Drugs used to prevent and treat CMV infection may contribute to the decrease in eGFR following transplantation
- Larger area under the curve CMV viraemia was associated with larger decline in eGFR
- Strategies for reducing use of chemoprophylaxis in patients at low risk of CMV infection may reduce the loss of kidney function
- Further, earlier diagnosis and treatment of emerging CMV infection may assist in reducing the loss of kidney function following transplantation

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