Transplant International

Transplant International ISSN 0934-0874

INVITED COMMENTARY

Pre-transplant serum level of CXCL9 as a biomarker of acute rejection and graft failure risk in kidney transplantation

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Received: 10 November 2009
Accepted: 10 November 2009

doi:10.1111/j.1432-2277.2009.01019.x

Kidney transplantation is the reference treatment for patients with end-stage renal disease. The advent of this therapeutic option has notably enhanced survival in patients with this disease. Nevertheless, morbidity and mortality remain much higher in transplant recipients than in the general population. Thus, today, effort has to be made to find more efficient treatments and to improve diagnosis. Moreover, there is a need to identify factors predictive of long-term graft outcome that could promote the implementation of a more personalized form of medicine. Chemokines are a group of small molecules that are known for their effect on cell trafficking. They also play fundamental roles in the development, homeostasis and function of the immune system [1,2]. They are divided into two major subfamilies, CXC and CC, based on the arrangement of two conserved cysteine residues separated by a single amino acid in CXC chemokines and adjacent in CC chemokines. Among them, CXCL9, CXCL10 and CXCL11 are T-cell and NK-cell chemoattractant molecules that have been shown to be abundant in the graft and to be regulated by interferon-γ. These chemokines are able to mediate pleiotrophic biologic functions. They are ligands of the CXCR3 molecule expressed by effector T cells infiltrating the allograft and have also been detected in biopsies with acute rejection [3,4]. Today, the exact role of CXCR3 and its ligands in organ transplantation remains unknown. MHC mismatched CXCR3$^{-/-}$ mouse recipients were shown to experience prolonged cardiac allograft survival for several weeks and even long-term survival when additionally treated with low doses of CsA for a few days [3]. These data provide new insight into CXCR3 and chemokine receptors as potential targets for novel therapeutic strategies in transplantation. Nevertheless, such results were not confirmed in fully mismatched allografts [5]. Moreover, Kwun *et al.* evaluated the effect of the CXCR3 receptor antagonist MLR-957 on cardiac allograft survival and of the anti-CXCR3 mAb in human CXCR3 knock-in mice and reported only a moderate increase in graft survival. He consequently concluded on a weak role of CXCR3 in allograft rejection and on a modest contribution of CXCR3 to leukocyte trafficking [6]. Thus, to date, the relevance of such a molecule and its ligands in human transplantation is still largely debatable [7].

Nevertheless, the question remains as to why CRCR3 as well as its ligands, CXCL9, CXCL10 and CXCL11, are so abundant in biopsies from patients with acute rejection. In their paper in this issue of Transplant International, Rotondi *et al.* did not question the mechanisms or involvement of chemokines and their ligands in organ transplantation, but retrospectively measured CXCL9 levels in pre-transplant serum samples collected from 252 kidney graft recipients. They reported that combined measurement of both pre-transplant CXCL9 and CXCL10 serum levels might represent a clinically useful parameter to identify subjects at high risk of acute rejection and graft failure. Why patients under standard or peritoneal dialysis have much higher CXCL9 levels than normal individuals is puzzling and comparison with values in

preemptive transplantation could bring information to light on a possible role of dialysis. The same analysis should also be performed in the future on hyperimmune patients (PRA > 20%) at the time of transplantation. Rotondi *et al.* also showed that CXCL9 is highly expressed in resident and infiltrating cells of kidney biopsies from subjects with acute rejection, particularly in vascular and tubular structures. The authors suggest that CXCL9 may be involved in the onset of chronic allograft dysfunction, renal fibrosis and ultimately graft loss. Analysis of pre-transplant donor biopsies would be informative, enabling speculation on its impact on the CXCL9 recipient response. These data corroborate a first paper from the same group published several years ago [8] as well as previous studies by other groups that already showed that urinary levels of CXCL9 may predict acute rejection [9].

The discovery of potential markers of graft outcome is a relevant goal in clinical transplantation. Non-invasive predictors would be useful even if used independent of the mechanistic role they may have in determining graft outcome. The objectives of these biomarkers in transplantation are to guide clinical decision-making and to adapt treatment for the patients. Different approaches have been used to discover such biomarkers: small-scale techniques such as flow-cytometry, ELISA, ELISPOT, cytotoxic T lymphocyte (CTL) assay and TCR repertoire analysis (see for review [10,11]). Recent technologically sophisticated techniques have also enabled large-scale screening such as genomics or proteomics (see for review [12,13]). In the present study, Rotondi *et al.* assessed the possibility of a combined elevated serum level of CXCL9 and CXCL10 in evaluating risk of graft failure prior to transplantation. A cut-off level for CXCL9 was established, which may be useful to identify candidates for kidney transplantation with higher immunological risk. Such results need to be confirmed in a larger randomized study with higher statistical power and require validation in multicentric, prospective trials. Whatever the technique used, the tendency today is to combine multiple parameters to create a score that would be more robust than for each parameter measured alone. It seems reasonable to suggest that combined pre-transplant serum levels of CXCL9 and-CXCL10 may be useful in such trials that have the potential to become routinely used in transplant centres and to improve the lives of graft recipients.

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