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Editorial Comment

EDITORIAL COMMENT

Looking for the needle in the kidney transplantation haystack

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Abstract

The diagnosis of acute rejection still relies on renal allograft biopsy. In fact, histological features including C4d staining can be useful to differentiate cellular and antibody-mediated acute rejection. However, the pathogenic mechanism to define the type of rejection is usually assessed by anti-HLA donor specific antibodies (DSA) monitoring. Suspicion of acute rejection is usually based on renal function deterioration. This method has low sensitivity. Moreover, creatinine increase follows graft injury and therefore the diagnosis is performed when there is an ongoing acute rejection. One strategy to overcome the limitation of serum creatinine as predictor of acute rejection is to perform surveillance protocol biopsies. However, the low incidence of subclinical acute rejection among patients treated with tacrolimus-based immunosuppression makes this procedure questionable in terms of cost-effectiveness. In this scenario new biomarkers predicting acute rejection are urgently needed. Ideally, such biomarkers should anticipate acute rejection, thus allowing preventive actions such as maintenance immunosupression intensification and/or modification. Alternatively, these new biomarkers should at least improve the predictive value of serum creatinine monitoring. Although many of the new biomarkers are promising, none have been translated to the clinic to date because of a lack of validation studies and the existence of major methodological concerns.

The diagnosis of acute rejection in kidney transplantation has been refined in the last two decades. Firstly, it has been recognized that, as well as clinical acute rejection (associated with rapid decline of glomerular filtration rate), there is also subclinical acute rejection [1] (without modification of glomerular filtration rate), and that both are associated with the development of chronic allograft lesions and worse graft survival [2]. Secondly, and probably most importantly, great progress in the identification of the pathogenic mechanisms (cell- or antibody-mediated) behind acute rejection has been achieved [3]. This information on the predominant immune effector mechanism involved in allograft damage provides transplant physicians with appropriate guidance to decide on the best therapeutic approach to prevent acute rejection. Finally, there has been a clear improvement in the proportion of acute rejection cases that are successfully treated [4].

In current clinical practice, the diagnosis of acute rejection still relies on renal allograft biopsy. In fact, histological features including C4d staining can be useful to differentiate cell- and antibody-mediated acute rejection [5]. However, assessment of the underlying pathogenic mechanism to define the type of rejection is usually conducted via the monitoring of anti-human leukocyte antigen donor-specific antibodies [6]. The most recent Banff classification for the diagnosis of acute rejection categorizes cell- or antibody-mediated acute rejection based on both renal histology findings and the assessment of donor-specific antibodies [7].

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In this issue of *Clinical Kidney Journal*, Hanssen *et al.* [8] and Erpicum *et al.* [9] review non-invasive approaches in the diagnosis of acute kidney allograft rejection. However, nowadays, 'the gold standard' ultrasound-guided kidney biopsy is considered a safe method [10], which in selected cases can be even performed as an outpatient procedure and thus at lower cost. Surprisingly, after many years of investigation, papers being published, conferences, editorials and the investment of a lot of money on non-invasive methods to diagnose acute rejection, no new methodology seems to be clearly superior to the 'old' serum creatinine approach. Up to now, history has constantly repeated itself in this way regarding new 'biomarkers' in renal transplantation: an eternal promise without further validation [11]. But, do we need such non-invasive methods for the diagnosis of acute rejection?

The unmet need in acute rejection is detection by biopsy rather than confirmation. In fact, suspicion of acute rejection is usually based on the estimation of deteriorating renal function by serum creatinine. This method has low sensitivity, as clearly illustrated in the definition of subclinical acute rejection. On the other hand, deterioration of renal function follows graft injury; therefore, the diagnosis is performed when there is an ongoing acute rejection. One strategy to overcome the limitations of serum creatinine as a predictor of acute rejection is to perform surveillance protocol biopsies [10]. However, the low incidence of subclinical acute rejection among patients treated with tacrolimus-based immunosuppression makes this procedure questionable in terms of cost-effectiveness [12]. Thus, protocol biopsies are recommended only in special transplant populations such as high immunological risk kidney allograft recipients.

In this scenario, new biomarkers predicting acute rejection are urgently needed [13]. Ideally, such biomarkers should anticipate acute rejection, thus allowing preventative actions such as maintenance immunosuppression intensification and/or modification. Alternatively, these new biomarkers should at least improve the predictive value of serum creatinine monitoring. However, this simple objective is challenging since there is always some risk of rejection associated with non-compliance/non-adherence and excessive minimization of immunosuppression by physician prescription [14]. After reading both exhaustive and comprehensive reviews on our current knowledge of non-invasive approaches in the diagnosis of acute rejection [8, 9], it can be concluded that, although many of these approaches are promising, none have been translated to the clinic to date because of a lack of validation studies and the existence of major methodological concerns. Thus, we are still looking for the needle (biomarker) in the kidney transplantation haystack. Perhaps it is time for us to move our attention from the problem and focus our studies on the individual or a homogeneous group of subjects who are at risk, rather than focusing on the whole transplant population. Intuitively, the smaller the haystack, the higher the likelihood of finding the needle.

CONFLICT OF INTEREST STATEMENT

None declared.

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