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Donor Derived Cell-free DNA: The Holy Grail for Non-invasive Diagnosis of Rejection?

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Editorial

While the incidence of acute rejection has declined considerably in the current era of potent immunosuppressive regimens, when rejection does occur, it continues to pose a significant management challenge. One of the more challenging aspects pertaining to renal allograft rejection is the difficulty in its early recognition and diagnosis. This stems from the fact that serum creatinine is not a sensitive marker for early rejection, and because of the poor specificity of rises in serum creatinine for rejection. The gold standard for diagnosis of rejection, therefore, remains a renal biopsy, which is invasive, and entails the use of additional resources and takes time. Because of this, much effort has been directed towards developing noninvasive biomarkers to diagnose and monitor for acute rejection. One such biomarker, that is gaining increased attention, is donor derived cell-free DNA. A spate of recent studies has investigated the use of this marker, not only to distinguish acute rejection from non-rejection in renal transplant recipients, but also to help assess the severity of acute rejection and response to treatment.

Most of the plasma cell-free DNA in a transplant recipient is of recipient origin, predominantly arising from the apoptosis of white blood cells. In the setting of allograft injury or inflammation, release of donor derived DNA into the plasma increases, theoretically making this an attractive biomarker for graft injury. As one might suspect, however, other causes of allograft injury, including pyelonephritis, ATN, and viral infections, by contributing to graft injury, have also been shown to increase plasma levels of donor derived cell-free DNA, reducing its specificity for rejection [1]; moreover, in the immediate post-transplant period, higher levels are seen, as a result of ischemia reperfusion injury [2]. Some investigators have also reported a very proportion of unexplained high donor derived cell-free DNA levels, when using previously published cut offs, calling into question the validity of this biomarker [1]. In one of the most widely cited studies, a prospective observational multicenter study, the plasma donor derived cell-free DNA level of 1% had a positive and negative predictive value for acute rejection of 61% and 84% respectively. The positive and negative predictive values for antibody mediated rejection at the same cutoff were 44% and 96% respectively. The median level was quite a bit higher with antibody mediated rejection at 2.9%, compared to T-cell mediated rejection where it was 1.2% and controls in whom the median level was 0.3%. Based on this, the investigators recommended using a threshold of greater than 1% to indicate the probability of acute rejection [3]. Other studies, similarly, have shown higher levels with antibody mediated rejection, and in fact found the biomarker to not have significant discriminative value in distinguishing cell-mediated rejection from no rejection [4].

Because of the concern that since much of the plasma cell free DNA is of recipient origin, reporting donor derived cell-free DNA as a fraction of the total cell-free DNA, may contribute to poor validity of the test due to the confounding effect of variations in the amount of recipient cell-free DNA from one moment to another, some investigators have assessed whether using the total copies/ml of donor derived cell-free DNA might improve test characteristics [2]. When compared to assessing donor derived cell-free DNA as a percentage, the use of the absolute number of copies/ml of donor derived cell-free DNA improves diagnostic accuracy for acute rejection. Using a cut-off of 52 copies/ml, the sensitivity and specificity for rejection were both 73%. Both tests have very high negative predictive value but the positive predictive value remains low. Last, but not least, because of the very short half-life of donor derived cell-free DNA (30 to 60 minutes), trends in donor derived cell-free DNA levels can possibly be of use in assessing response to rejection treatment, potentially obviating the need for repeat renal biopsies [5].

So where does this leave us? Clearly, larger studies are needed to better identify the niche that this potentially useful biomarker might have in the management of patients suspected of having acute rejection. Most of the aforementioned studies have been limited by small study sizes. There also seem to be varying thresholds and cutoffs used in the reported studies, which need to be reconciled. Lastly, the greatest value of this biomarker might be in ruling out rejection, and in following response to therapy in patients who already have an established diagnosis of rejection, unless refinements in techniques lead to increase the sensitivity and positive predictive value of these biomarkers. Until then, the search for the Holy Grail continues.

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