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EDITOR'S NOTE

Dr Manoj Durairaj

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Greetings dear Readers.

This issue of The Revival features the current status of Non-Invasive modalities for the surveillance of post Cardiac transplant Allograft Rejection. Our guest author is Dr Kishore Gupta, who is a Consultant Cardiac Surgeon at Marengo CIMS Hospital, Ahmedabad.

These Non-Invasive modalities will have a crucial role to play in our surveillance strategy in the future and may become standard of care especially in centres where in endomyocardial biopsies cannot be performed at regular intervals due to various financial and technical constraints. A detailed echocardiography at 2-3 monthly intervals, in addition to regular clinical assessment have played a crucial role in picking up early signs of rejection in my practice.

Through a comprehensive evaluation of donor-derived cell-free DNA, gene expression profiling, microRNA analysis, donor-specific antibodies, and magnetic resonance imaging, this article aims to illuminate the potential of these non-invasive diagnostic modalities for allograft rejection surveillance post cardiac transplantation. By harnessing the power of these innovative approaches, lets aspire to enhance patient care, optimize outcomes, and advance the field of heart failure and transplantation.

I thank Dr. Gupta for this informative article and wish our Readers a Happy Reading as always.

Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr Talha Meeran

MBBS, MD, FACC,
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Dear Colleagues,

The April issues for REVIVAL features an excellent review on non-invasive surveillance methods for cardiac allograft rejection post transplant. Dr Kishore provides an in-Depth literature review on all the modalities for rejection surveillance enlisting the shortcomings and advantages of each method. Donor derived cell free DNA is a promising modality for rejection surveillance. However we still need further validation of cell free DNA in larger cohorts particularly in an Indian scenario before it becomes part of routine practice in India

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

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Special thanks to Dr Kishore Gupta for authoring this month's article.

Designed by Maithili Kulkarni

PRESIDENTIAL MESSAGE

Dr. Julius Punnen

Sr. Consultant Cardiothoracic Surgeon, Narayana Health, Bangalore

Dear members of SfHFT,

As the President of the Society for Heart Failure and Transplantation, it is my honour to introduce an insightful article titled "**Role of non-invasive diagnostic modalities for allograft rejection surveillance post cardiac transplantation**." In this article, the author delves into the pivotal role of non-invasive diagnostic modalities in the surveillance of allograft rejection following cardiac transplantation, with a specific focus on donor-derived cell-free DNA, gene expression profiling, microRNA, donor-specific antibodies, and magnetic resonance imaging (MRI).

Cardiac transplantation has revolutionized the management of end-stage heart failure, providing a lifeline to countless patients worldwide. However, the risk of allograft rejection remains a significant challenge in the long-term care of transplant recipients. Traditionally, endomyocardial biopsy (EMB) has served as the gold standard for diagnosing rejection episodes. Nonetheless, the invasive nature of EMB, along with its limitations, has spurred the exploration of non-invasive alternatives. The need for non-invasive rejection surveillance became more pronounced during the COVID pandemic when patients were not able to come to hospitals for procedures either because the hospitals were fully occupied with COVID patients or for the protection of post – transplant patients from being infected.

Donor-derived cell-free DNA (dd-cfDNA) has emerged as a promising non-invasive biomarker for allograft rejection surveillance. This circulating DNA, originating from the transplanted heart, can be quantified in the recipient's blood. Monitoring dd-cfDNA levels allows for early detection of rejection episodes, potentially enabling timely intervention and improved patient outcomes. The article will delve into the principles, performance characteristics, and clinical utility of dd-cfDNA in in detail.

Gene expression profiling has also garnered significant attention in the field of cardiac transplantation. By assessing the expression levels of a panel of genes associated with rejection, it is possible to generate a gene expression profile score that aids in identifying patients at risk of rejection. We will explore the current evidence regarding the utility of gene expression profiling in allograft rejection surveillance and discuss its potential integration into routine clinical practice.

MicroRNAs (miRNAs), small non-coding RNA molecules, have demonstrated remarkable potential as biomarkers in various disease states. In the context of cardiac transplantation, specific miRNA signatures have shown promise in distinguishing between stable graft function and rejection episodes. The article examines the emerging evidence surrounding miRNAs as non-invasive tools for allograft rejection surveillance, highlighting their diagnostic accuracy and potential for prognostication.

Donor-specific antibodies (DSAs) play a crucial role in allograft rejection and graft loss. Non-invasive monitoring of DSAs can aid in the early detection of antibody-mediated rejection. By discussing the evolving landscape of DSA detection and monitoring techniques, the author aims to shed light on their potential in allograft rejection surveillance post cardiac transplantation.

Lastly, the article explores the role of magnetic resonance imaging (MRI) in the non-invasive assessment of cardiac allografts. Advanced imaging techniques, such as T2-weighted and late gadolinium enhancement imaging, offer valuable insights into myocardial inflammation, fibrosis, and edema. These imaging modalities hold promise as non-invasive tools for allograft rejection surveillance, providing detailed structural and functional information without the need for invasive procedures.

I express my utmost gratitude to the author whose contributions have enriched this article, and I extend my appreciation to the entire scientific community for their unwavering commitment topushing the boundaries of medical knowledge in pursuit of improved patient outcomes.

With warm regards,

Julius Punnen

President, Society for Heart Failure and Transplantation

ROLE OF NON-INVASIVE DIAGNOSTIC MODALITIES FOR ALLOGRAFT REJECTION SURVEILLANCE POST CARDIAC TRANSPLANTATION

ABOUT THE AUTHOR

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Following his surgical training of DNB CTVS at Fortis Healthcare Mohali under the esteemed guidance of Dr. TS Mahant, he joined as a Consultant Cardiothoracic Surgeon at Marengo CIMS and has been an important part of Cardiac surgery transplant team led by Dr. Dhiren Shah. He has authored and co-authored numerous review and research articles in reputed national and international journals. Areas of interest include heart transplantation and total arterial revascularization.

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Introduction

Heart transplant is the established treatment for end stage heart failure since many years. Surveillance of allograft rejection and allograft injury post transplantation is one of the most indispensable factors which determines the survival outcomes, transplant longevity and patient survival. The first year after heart transplantation has 40% incidence of rejection episodes. 20% of the reported rejections are "biopsy negative" [1-2]

Till date endomyocardial biopsy (EMB) has remained the "gold standard" method of monitoring for rejection, despite the procedural discomfort and rarely associated serious complications. (8-16) The strengths and utility of EMB is limited by its invasiveness, cost limitations, noticeable profile of complication. Hence, there remains an unmet need for a less invasive and more accurate approach for diagnosing or ruling out allograft rejection after transplant. [3-4]

There are certain non-invasive diagnostic modalities which can aid in acute cardiac allograft rejection (ACAR) and can avoid or at least curtail the unnecessary number of biopsies in post-transplant period.

Cell free DNA

Cell-free DNA is 'extracellular' DNA (cf-DNA), found in blood originated from cardiomyocyte damage due to allograft rejection or injury. [5] cf-DNA is rapidly becoming a highly useful tool for surveillance of solid organ transplant rejection. It is evident that high amounts of graft-derived cfDNA are released into the bloodstream during rejection.

cf-dDNA fraction is elevated on post-transplant day 1, but gradually reduce to steady-state baseline levels by 7–10 days post-transplant, if there is no acute rejection. An increase in cfDNA levels is seen both in infection and rejection. Baseline plasma levels vary according to the type of solid organ transplantation and are directly proportional to the transplanted cell mass.

First cell free DNA assay was licensed under the name 'Allosure' uses 405 SNP panel, also known as standard SNP test. The Expanded SNP test 'Prospera' utilizes 13,292 highly polymorphic SNPs has also been clinically validated for rejection surveillance. [6] Both assays were similar in terms of test efficacy. However, in a recent study, combination of Gene Expression Profiling (GEP) with standard SNP commercially packaged as HeartCare® (CareDx; Brisbane, California) showed significantly lower specificity when compared to either standard or expanded SNP dd-cfDNA tests individually. [7]

The Donor-Derived Cell-Free DNA-Outcomes AlloMap Registry (D-OAR) study which was done across 26 centres in US showed that dd-cfDNA levels were correlated to paired events of biopsy-based diagnosis of rejection. A 0.2% threshold dd-cfDNA had a 44% sensitivity to detect rejection and a 97% negative predictive value. [8]

Similarly Genomic Research Alliance for Transplantation (GRAfT) study found that dd-cfDNA was strongly associated with Acute rejection with a high area under the receiver operating characteristic curve (AUC-ROC) and a high negative predictive value (NPV). Elevations in ddcfDNA preceded both forms of acute rejection, but are much earlier in antibody mediated rejection (AMR) than in acute cellular rejection (ACR), suggesting its sensitivity to detect allograft injury weeks to months before current clinical tools. [9] Though elevations are sensitive for graft injury, but not specific for the cause of injury, as they are also seen elevated in concomitant viral infections, EMB procedure, strenuous exercise, inflammatory diseases and malignancies. [10-11]

Cf-DNA seems a promising diagnostic modality for the future but certain limitations like standardisation of baseline cf-DNA levels in population, cf-DNA fraction association with other conditions need to be addressed. Certain trials are ongoing which can answer the questions and may increase the role of cf-DNA in surveillance management for ACAR.

The non-invasive surveillance strategy of expanded dd-cfDNA testing will be evaluated in an upcoming 'DETECT' trial and role of standard dd cf-DNA + GEP in the 'MOSAIC' trial. Few other trials (BIODRAFT, SHORE) are also in progress which can unfold the exact role and contribution of cfDNA in immunosuppression tailoring and rejection surveillance.

GEP

Quantitative assessment of mononuclear-cell gene expression in peripheral-blood specimens is another method for detecting the rejection of a cardiac transplant.[12-13] ALLOMAP, the first approved non-invasive gene-expression profiling test showed ability to discriminate acute cellular rejection from quiescence in cardiac transplant recipients in a US population. (CARGO study) [14-15]

For the GEP test, a whole blood sample should be collected into Vacutainer with sodium citrate anticoagulant. Peripheral blood mononuclear cells are then isolated, lysed by RNA lysis test (RLT) buffer and the released ribonucleic acid (RNA) is stabilized and purified. Finally complementary deoxyribonucleic acid (cDNA) is generated for use in the GEP test. Real-time polymerase chain reaction (RT–PCR) is used to quantitate expression levels of a preselected panel of 20 genes which gives a GEP logarithmic score that ranges from 0 to 39. The test has an excellent NPV of 99%, but poor PPV of ~10% for ACR and has no ability to detect AMR.

Recipients two months post-transplant period, 30 days after transfusion of blood products, 3 weeks after administration high prednisone doses and 2 months after treating a prior rejection fulfil the inclusion criteria for GEP testing.

Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial showed a score below 34 as cut-off in low-risk patients resulted in significantly fewer biopsies. GEP group showed lesser sensitivity but no difference in cumulative risk of graft dysfunction. [16] Cargo II trial were also similar to the CARGO study.

There are certain limitations of GEP scoring which includes higher

scores in the presence of CMV infection and lower specificity in comparison to standard SNP cf-DNA test. [17-18]

Micro RNA

MicroRNAs (miRs) are highly-conserved, noncoding, small (»22 nucleotide) sequences that negatively regulate gene expression and are promising genomic biomarkers in cardiovascular medicine with the ability to detect heart transplant rejection. [19-20] MicroRNAs have recently emerged as relevant candidates in the field of organ rejection because of their capacity to regulate thousands of genes that are key elements of both innate and adaptive immune responses.[21] Various miRNAs are of potential clinical interest as non-invasive biomarkers of heart transplant rejection which showed differential tissue expression between rejecting and normal heart allografts.

The Genomic Research Alliance for Transplantation (GRAfT) study was a multicentre prospective cohort study that phenotyped heart transplant patients from 5 mid-Atlantic centres identified novel miRs that are differentially regulated with ACR and AMR and were independently validated.

miRNAs miR-10a, miR-155, miR-31, and miR-92a were specific for inflammatory burdens in endothelial cells, inflammatory pathways, cardiomyocytes/interstitial cells, and endothelial cells, respectively but miR-10a and MiR-92a are mainly expressed in heart allograft endothelial cells, which are the primary target for the alloimmune response.

Duong Van Huyen and colleagues reported 14 preselected miRs that were characterized in the serum and EMB tissue specimens of heart transplant patients with ACR and AMR using RT-PCR. [22] Constanso-Conde identified miR-181a-5p as a potential biomarker of ACR.

MRI

Cardiovascular magnetic resonance (CMR) imaging– based myocardial tissue characterization with T1 and T2 mapping has emerged as a non-invasive and highly sensitive method of detecting cardiac allograft rejection. CMR offers a diagnostic advantage in detection of edema, inflammatory transformation, development of fibrosis, and forecast of mortality through volumetric estimation of ventricles using quantitative T1 and T2 weighted techniques.[23]

Myocardial native T1 time reflects both intracellular and extracellular signals and is elevated with fibrosis and inflammation. T1 mapping–based extracellular volume fraction is more representative of the extracellular space alone but requires gadolinium administration. T2 mapping–based myocardial T2 time is reflective of myocardial edema and inflammation and is well validated in cardiac allograft rejection.[24]

Standardized T1 and T2 mapping values for normal population are 900 to 1,020 milliseconds and 43 to 55 milliseconds, respectively, at 1.5 Tesla.[25]

Using T1 with contrast, extracellular volume fraction (ECV) can be calculated, which has been found to correlate with rejection. T2 relaxation time, T2 short time inversion recovery intensity, T1 myocardial contrast enhancement, late gadolinium enhancement (LGE), and peak systolic CS are five parameters of CMR that were applied in different studies to detect moderate ACAR. Out of these parameters, T2 value related to myocardial edema is the most widely used parameter. Imran et al. demonstrated an excellent negative predictive value of T1 mapping for cardiac allograft rejection.[26]

In Paediatric heart transplant patients, higher native T1 values were observed as compared to controls without transplants and higher native T2 values in cases of allograft rejection.

Patients with acute rejection have higher T2 levels and higher extracellular volume fraction (ECV).[27] Increasing T2 values are associated with worsening left ventricular function and increasing T1/ECV values with rejection history and low-grade CAV.

ECV is a technique for measurement of interstitial expansion, reflecting diffuse myocardial fibrosis and edema due to an acute or chronic cardiovascular insult, such as ACAR. Unlike T2, ECV is not elevated in recipients with history of ACAR, making it superior to T2 at distinguishing active ACAR, especially in patients with significant history of ACAR. ECV may be as effective or superior to T2 for detection of ACAR, but it requires intravenous contrast, which is contraindicated in many patients, most commonly due to concomitant renal dysfunction.

To conclude, a combined CMR approach using T2 mapping and ECV quantification provides a high diagnostic accuracy for acute rejection diagnosis and could potentially decrease the number of routine EMB.

DSA

Donor-specific antibodies (DSAs) are antibodies formed by the recipient that can bind to the donor organ, triggering activation of the complement cascade and resultant allograft injury.

Up to 30% HT recipients develop de novo DSA. DSA against class II HLA predominate (>50%), followed by DSA to both class I and II HLA (up to 30%), while isolated class I HLA DSA are less frequent (<20%). Early post-transplant detection (<3 months) of DSA could be either due to resurgence of preformed antibodies developed before HT that were not detected due to low levels, or due to formation of new DSA.

Persistent de novo DSA (>30 days on repeat testing) have significantly higher mortality compared to those who have no or transient de novo DSA.[28] Serial interval monitoring of DSA is required to differentiate transient from persistent and early occurring from late appearing DSA. The International Society of Heart and Lung Transplantation recommends routine HLA antibody screening at 2 weeks, 1-, 3-, 6-, and 12-months post-transplant and annually thereafter with more frequent monitoring (every 3-6 months) for high-risk recipients with prior

DSA, rejection and allograft dysfunction.[29]

Antibodies to non-HLA antigens such as antiangiotensin II type 1 receptor (AT1R), anti-vimentin antibodies, antiendothelial -1 type A receptor antibodies and anti-MHC I-related chain antibodies have been proposed to result in acute and chronic AMR in HT recipients.

Table 1 shows the summary of recent guidelines for rejection surveillance updated in year 2023.

BLOOD TROPONIN and BNP

Cardiac troponins T and I are exclusively present in cardiomyocytes and are highly sensitive and specific markers of myocardial injury.

N-terminal pro-brain natriuretic peptide (NT-proBNP) reflects increased ventricular wall stress, pressure and is a well-known diagnostic and prognostic marker in heart failure. The clinical utility in allograft is very little and is limited by non-specificity of the biomarker.

2010	LOE	2023	LOE
EMB in a HT candidate suspected of having an infiltrative cardiomyopathy or an inflammatory process	IIa, C	Same	Same
EMB during the first 6 to 12 postoperative months for surveillance	IIa, C	Periodic EMB during the first 3 to 12 postoperative months for surveillance	IIa, C
Utilize echocardiography in younger children	IIa, C	use a combination of noninvasive screening methods (echocardiography, ECG, biomarkers) instead.	IIa, C
EMB surveillance for high-risk patients	II, C	Same	IIa, C
EMB 5 years after HT	IIb, C	Not recommended	III, B
Ventricular evoked responses (VER) monitoring for rejection surveillance	IIa, C	Not recommended	III, C
Gene Expression Profiling between 6 months and 5 years after HT, ACR of grade 2R or greater	IIa, B	Between 2 months and 5 years	IIa, B
Electrocardiography for surveillance	III , C	Same	Same
Echocardiography as an alternative to EMB	III, C	May be an acceptable in low risk and when EMB not possible	IIb, C
MRI for acute allograft rejection	III, C	Adjunct modality in patients with unexplained graft dysfunction and low-grade or absent histologic evidence of rejection on EMB.	IIb, C
		DSA should be performed at 1, 3, 6, and 12 months postoperatively and annually thereafter.	IIa, C
Systemic inflammatory markers	III, C	Same	Same
Non-invasive testing modalities	III, C	For younger	IIa, C
		Immune cell function assay (ImmuKnow)	III, B

Table 1 The summary of recent guidelines for rejection surveillance updated in year 2023

Conclusion:

Developing non-invasive methods for rejection surveillance are of utmost need in the current scenario to replace or at least minimise the existing invasive and more expensive EMB technique. The current evidence points out that the blood-based modalities have high negative predictive value and are sensitive for antibody mediated rejection. Whereas, the cardiac MRI and miRNA is more sensitive for acute cellular rejection surveillance. More clinical studies are needed to standardise the cut-off values and replicate the results in paediatric population and various demographic subsets to form strong evidence in terms of clinical superiority over the invasive diagnostic methods. Only then in the coming time, the non-invasive diagnostic modalities can play the pivotal role in the field of cardiac transplantation.

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