Society for Heart Failure and Transplantation

SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

THE REVIVAL

Promoting Academics to Improve Clinical Outcomes.

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EDITOR'S NOTE

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Dear Readers of the Revival,

Greetings!

Dr. Chintan Sheth's last installment on transplant immunology delves into the critical post-transplant phase, offering invaluable insights into managing graft-related complications. By exploring the development and implications of de novo DSA, the article sheds light on key risk factors and clinical considerations for enhancing patient care. Moreover, Dr. Sheth elucidates emerging non-invasive techniques like cell-free DNA analysis, providing clinicians with novel tools for rejection surveillance and diagnosis. The discussion on Allomap underscores its utility in predicting acute cellular rejection, albeit with limitations in detecting antibody-mediated rejection. Overall, this issue underscores Dr. Sheth's expertise and the significance of his contributions in advancing transplant medicine. I thank him on behalf of the Editorial Board for his 4 part series on Heart Transplant Immunology.

Wishing our dear Readers a Happy Reading!

Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR

Dr Talha Meeran

MBBS, MD, FACC,
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Dear Colleagues,

This edition of REVIVAL is the last in a series of four review articles by Dr Chintan Seth focusing on transplant immunology. The current issue of REVIVAL focuses on the role of DSAs and the mechanism of formation of DSAs in the post-transplant surveillance for rejection. Positive DSAs have been shown to consistently negative impact post-transplant outcomes. However, not all DSAs are harmful and tests measuring the ability of these antibodies to activate the complement system(C1q assays) may be helpful in discerning the difference. The section of cell free DNA is a brief yet succinct summary of this important and rapidly developing field of transplant surveillance. Allomap has been an important part of the armamentarium of transplant teams in western world for several years now however it remains conspicuous by its absence in India.

Sincerely,
Dr Talha Meeran
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Special thanks to Dr Chintan Sheth for authoring this month's article.

Designed by Maithili Kulkarni

PRESIDENTIAL MESSAGE

Dr Julius Punnen

Sr. Consultant Cardiothoracic Surgeon, Narayana Health, Bangalore

Dear Members and Colleagues,

In this edition of the Revival, we have the final installment of the review of transplant immunology by Dr. Chintan Sheth, an expert Cardiac and Heart & Lung Transplant Anesthesiologist and Cardiac Critical Specialist. In the prior issues of the Revival, Dr. Sheth described basics of transplant immunology, immune responses, its clinical implications, notably, cellular and antibody-mediated rejection and testing techniques used in immunological evaluation pre-transplant and at the time of transplant. In this part, he highlights the importance of immunology in post-transplant management, including surveillance for donor-specific antibodies (DSA) and rejection surveillance using newer, innovative techniques.

De novo DSAs post-heart transplantation represents a significant concern, as these can lead to cardiac allograft damage and rejection. Various risk factors, including recipient demographics, viral infections, HLA mismatching, and non-adherence to immunosuppressant medications, contribute to the development of de novo DSA. DSAs mediate graft injury via complement activation, vascular endothelium damage and activation of proinflammatory cells and cytokines.

The endomyocardial biopsy (EMB), which is the traditional gold standard, remains crucial for detecting acute cellular rejection (ACR) and antibody-mediated rejection (AMR). However, the limitations of this method, including the potential for false negatives, inter observer variability, need for an invasive procedure, with its inherent risk profile, underscore the need for complementary approaches. The introduction of cell-free DNA, known as liquid biopsy, has emerged as a promising non-invasive method for rejection surveillance.

Donor-derived cell-free DNA (ddcfDNA) is released into the recipient's circulation when allograft cells die, providing a unique opportunity for rejection detection. The AlloSure assay, utilizing ddcfDNA, has demonstrated its efficacy in distinguishing rejection from a quiescent state. It has a high sensitivity and specificity, for both ACR and AMR. The liquid biopsy approach offers several advantages, including early detection of rejection, reliable and reproducible results and forgoing the need for an invasive procedure.

While the potential of liquid biopsy is groundbreaking, questions remain, and large multicenter trials are needed to address these uncertainties. Nevertheless, the rise of ddcfDNA before histopathologic evidence of rejection, positions liquid biopsy as a valuable tool in the rejection surveillance arsenal.

In parallel, Allomap, a non-invasive peripheral gene expression test, has a high negative predictive value and specificity for ACR but a low positive predictive value and sensitivity, as demonstrated in the CARGO and CARGO II studies. The Allomap has also demonstrated equivalence to EMB with regards to clinical outcomes post-heart transplant recipients in the IMAGE and EIMAGE trials. It is also useful to guide corticosteroid weaning. However, its limitations in detecting AMR highlight the need for a comprehensive approach that incorporates evolving technologies like ddcfDNA.

The future of post-transplant surveillance lies in embracing a multi-faceted strategy that combines traditional methods with innovative approaches. Liquid biopsy and advanced gene expression testing are paving the way for more precise, timely, and non-invasive rejection detection. As we navigate this evolving landscape, ongoing research and collaboration will be key in refining these techniques and improving outcomes for transplant recipients.

In conclusion, the field of post-transplantation monitoring is undergoing a transformative phase, with liquid biopsy and Allomap presenting exciting possibilities. These advancements have the potential to revolutionize the way we detect and manage rejection, ultimately enhancing the long-term success of heart transplantation. As we move forward, a holistic and integrated approach to rejection surveillance will be vital in ensuring the best possible outcomes for heart transplant recipients.

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With warm regards,

Dr Julius Punnen

President, Society for Heart Failure and Transplantation

TRANSPLANT IMMUNOLOGY-
CLINICAL IMPLICATIONS (PART - IV)

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Working as a Consultant Cardiac and Heart & Lung Transplant Anesthesiologist And Cardiac Critical Specialist at Marengo CIMS Hospital for 12 years.

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Did DA (Diploma Anesthesia) from Stanley Medical College, Chennai in 2008 and DNB anesthesia from Narayana Hrudayala, Bangalore in 2010.

Fellowship in Cardiac Anesthesia (FICA) from Narayana Hrudayalaya, Banglore under Dr. Muralidhar Kanchi in 2011.

Continued from Part Iii

Post-transplant

De novo DSA post-transplantation screening

The antibodies that do not pre-exist but develop after transplantation and are directed against foreign graft HLA are considered as de novo anti-HLA DSA. Approximately 10–30% of heart transplant recipients developed de novo DSA (predominantly anti-HLA class II) after transplantation12. The independent risk factors that have been identified to develop de novo DSA have included female sex of the recipient, young age of the recipient, viral infection (especially cytomegalovirus and Epstein-Barr virus), class II HLA mismatching, prior cellular rejection, sensitizing events (blood transfusion, retransplantation, pregnancy, etc.) and non-adherence to immunosuppressant medication. The main mechanisms by which DSA mediate graft damage include (Figure:10):

(1) complement activation via the classical pathway and the resultant formation of the membrane attack complex (MAC), as evidenced by the presence of C1q, C4d and C3d at the site of complement activation

(2) direct and indirect damage to vascular endothelium through their interactions with HLA and/or non-HLA antigens expressed on cell surface

(3) activation of proinflammatory cells such as natural killer (NK) cells, macrophages and neutrophils, which are involved in inducing injury of vascular endothelium.

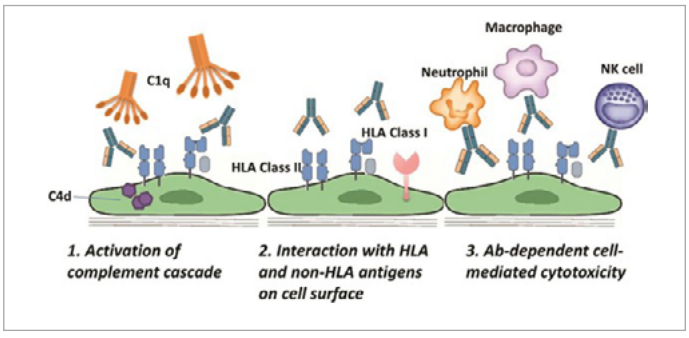

Figure 10: Mechanism of formation of DSA

Figure 10 Courtesy: Wang J, Wang P, Wang S, Tan J. Donor-specific HLA Antibodies in Solid Organ Transplantation: Clinical Relevance and Debates. Explor Res Hypothesis Med. 2019;4(4):76-86. doi: 10.14218/ERHM.2019.00012.

CLINICAL PEARLS

1. EMB is the still gold standard for diagnosis of both ACR and AMR of heart transplant rejection. Presence of DSA gives idea about the presence of AMR. Sometimes biopsy report is negative may be due to biopsy tissues is limited portion of the heart myocardium and cannot represent whole myocardium but if patient is symptomatic with LV or RV dysfunction on ECHO and presence of DSA should be treated as AMR. So every time when in doubt or even for surveillance DSA should be done along with EMB.
2. DSA is of 2 types. Non complement fixing (associated with less mortality and complement fixing (C1q DSA). recent larger study showed worse 3-year survival in patients with asymptomatic complement-fixing DSA despite treatment with IVIG and rituximab.
3. De novo anti-HLA DSA post-transplantation is associated with a 1.8-fold increase in mortality and a 2.5-fold increase in MACE (major adverse cardiac events), with most of the separation in time to first MACE occurring early after the detection of DSA.
4. As complement activation initiated by C1q crosslinking of IgG bound to the allograft, it is hypothesized that DSA with high capability of binding C1q may confer the highest risk of graft injury.
5. C4d is an important component of the complement cascade, and thus is considered as a marker of complement regulation. Detection of DSA together with typical C4d deposition along myocardial capillaries was thought of as the gold standard technique to detect complement activation and AMR. over time it has been realized that C4d is neither completely specific nor sufficiently sensitive for the diagnosis of AMR. C4d alone may not be sensitive enough to establish a diagnosis of acute AMR.
6. Appearance of DSA (from serum sample), C4d deposit, and microvascular injury may represent great risk for hemodynamic instability, graft dysfunction, and ultimately graft failure.

Cell free DNA / Liquid Biopsy

Donor-derived cell-free DNA (ddcfDNA) is a new non-invasive approach to detect rejection that may improve on peripheral gene expression testing.

When allograft cells die, they release short DNA fragments (ddcfDNA – donor derived cell-free DNA) into the recipient circulation. Through sequencing and single nucleotide polymorphism assessment, ddcfDNA fragments are easily identified and quantitated13. The percentage of ddcfDNA (%ddcfDNA) describes the amount of ddcfDNA compared with the total cell-free DNA (cfDNA) found in the blood.

Currently, one ddcfDNA assay (AlloSure, CareDx, Inc) is available for clinical use through the Surveillance HeartCare Outcomes Registry (NCT03695601). This assay was assessed in a previous transplant registry (Donor-Derived Cell-Free DNA-Outcomes AlloMap Registry), and the level of ddcfDNA was significantly higher in patients with ACR or AMR than in those with no evidence of rejection on EMB.

At a cutoff of 0.2%, the ddcfDNA assay had 80% specificity and 44% sensitivity to differentiate acute rejection from no rejection, earning ddcfDNA the moniker of "the liquid biopsy."

ddcfDNA measures vary between antibody-mediated rejection and acute cellular rejection in lead time, quantitative levels, and cell-free DNA fragment type/ length. This provides a framework to use ddcfDNA to differentiate antibody-mediated rejection and acute cellular rejection.

Starting at 28 days after heart transplant, the use of a liquid biopsy with a ddcfDNA threshold of ≥0.25% had excellent sensitivity and specificity for diagnosis of rejection, safely avoiding 81% of all surveillance endomyocardial biopsies.

%ddcfDNA is reliable and reproducible, varies both quantitatively and qualitatively in AMR and ACR, has excellent biomarker performance characteristics, and unmasks pathology earlier than existing tools like EMB14.

The rise in ddcfDNA occurred before histopathologic evidence of rejection in AMR but not ACR. In 80% of cases of AMR, the rise in ddcfDNA was detected 3.2 months before diagnostic changes on EMB, whereas in ACR, the rise in ddcfDNA was coincident with changes on EMB in ?90% of cases. These observations provide evidence of the first noninvasive assay with the ability to distinguish between these 2 forms of rejection: a true "liquid biopsy."

Few studies offers the potential rationale for ddcfDNA to someday be incorporated into the routine rejection surveillance algorithm for heart transplant recipients (Figure 11). However, as with any good study, these findings raise as many questions as they answer. Till all these questions are answered by large multicentre trials, EMB is the gold standard for Diagnosis of rejection.

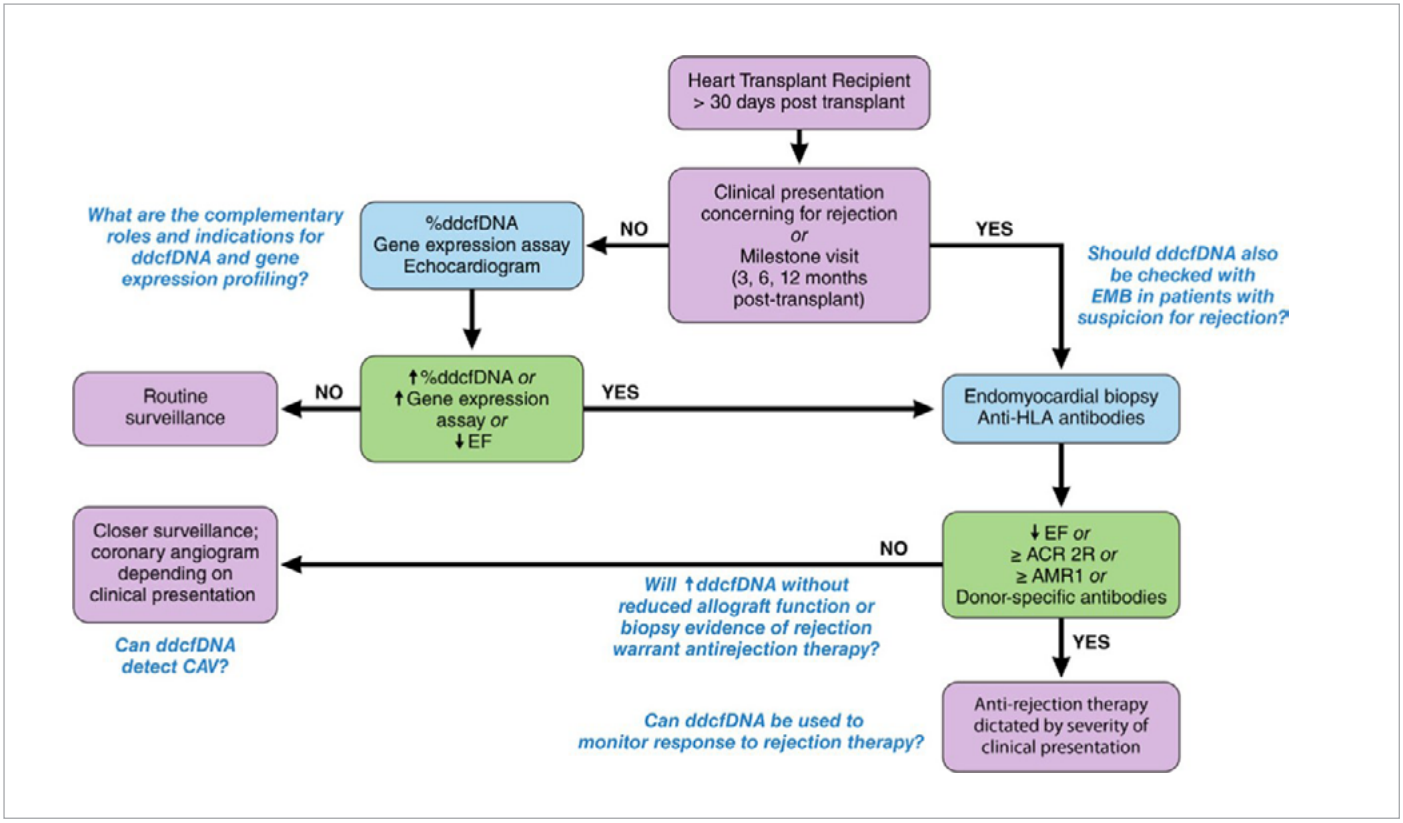

Figure 11: Algorithm to use ddcfDNA for rejection surveillance

Figure 11 courtesy: Solid Gold, or Liquid Gold? Towards a New Diagnostic Standard for Heart Transplant Rejection, Michelle M. Kittleson and Sonia Garg Originally published 22 Mar 2021 Circulation. 2021;143:1198–1201

Allomap

Non-invasive peripheral gene expression testing with a 99% negative predictive value for acute cellular rejection (ACR; AlloMap, CareDx, Inc).

However, peripheral gene expression with Allomap testing offers limited positive predictive value for ACR and was not designed to detect antibody-mediated rejection (AMR), a major barrier as the treatment, surveillance, and prognosis of AMR differ greatly from ACR.

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