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Beyond traditional therapies: Immune system targeting as a novel approach in heart failure management

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ABSTRACT

This review examines immune modulation as an innovative strategy for managing heart failure (HF), considering the shortcomings of conventional treatments in targeting inflammation that plays a critical role in Heart failure progression. Heart failure is increasingly acknowledged as being affected by chronic inflammation, which is fueled by cytokines and immune cell abnormalities, resulting in detrimental cardiac remodeling and compromised heart function. Emerging therapies aim to alleviate inflammation by focusing on pathways involving cytokines such as IL-1, IL-6, and TNF-α, as well as modulating immune cells like macrophages and T-cells. Combining these therapies with established Heart failure treatments and employing precision medicine for tailor-made strategies may lead to better outcomes and a transition toward individualized Heart failure care. Additional research is essential to fine-tune these strategies, ensuring effective immune modulation while preserving immune defense mechanisms.

KEYWORDS

Heart failure treatment; Chronic inflammation; Personalized heart care; Macrophage and T-cell modulation

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Introduction

Heart failure (HF) remains a critical public health challenge, contributing significantly to global morbidity and mortality. Affecting over 64 million people worldwide, it presents a complex clinical syndrome characterized by insufficient cardiac output to meet the body's demands, often leading to severe functional limitations and reduced quality of life. Despite advances in pharmacological and device-based therapies aimed at improving heart function, these interventions primarily address symptoms and slow disease progression rather than reversing cardiac damage or modifying underlying disease mechanisms. As a result, the long-term prognosis for many HF patients remains poor, with frequent hospitalizations and high mortality rates persisting across patient populations [1].

Emerging research highlights the limitations of traditional HF therapies, particularly as they do not adequately target the inflammatory and immune dysregulation central to HF pathophysiology. Inflammation is increasingly recognized as a core driver in the progression of HF, particularly in patients with comorbid conditions such as diabetes or ischemic heart disease. Inflammatory signals and immune cell dysfunction contribute to adverse cardiac remodeling, fibrosis, and impaired contractility, thereby worsening heart function and clinical outcomes [2,3].

Recent advancements in immunomodulation strategies provide a promising, novel approach by targeting immune pathways to mitigate inflammation and promote tissue repair. By focusing on specific immune cells and signaling molecules involved in HF progression, therapies aimed at modulating immune responses offer the potential for better outcomes beyond the capabilities of conventional treatments [3,4]. This review will examine the role of immune system targeting in HF, explore the mechanisms through which immune modulation may impact HF progression, and discuss the emerging therapies that harness the immune system for effective heart failure management.

Pathophysiology of Heart Failure and Inflammatory Mechanisms

HF is a complex syndrome arising from structural and functional cardiac abnormalities that lead to inadequate perfusion of organs. Key drivers of HF progression include chronic inflammatory processes that cause adverse cardiac remodeling, fibrosis, and impaired contractility. Initially, the heart compensates for increased stress by activating neurohormonal systems like the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). However, prolonged activation of these pathways leads to excessive oxidative stress and further damage, perpetuating the heart's dysfunction [5,6].

Role of inflammation in heart failure

Chronic inflammation is recognized as a central contributor to HF, driving both disease onset and progression. When myocardial injury occurs, immune cells are recruited to the site to clear damaged cells and promote healing. However, in HF, unresolved inflammation results in persistent immune cell activation, contributing to progressive damage. Elevated levels of inflammatory markers like C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are frequently observed in HF patients, underscoring the systemic inflammatory state associated with the condition [7].

Key inflammatory pathways in heart failure

Several inflammatory pathways play a role in HF. IL-1 is a pivotal cytokine that initiates the inflammatory response,

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enhancing immune cell recruitment and amplifying the release of additional cytokines. Elevated IL-6 levels correlate with worse HF outcomes, as IL-6 promotes fibrotic changes that compromise myocardial flexibility [8]. TNF-α is another critical cytokine, involved in increasing myocardial cell apoptosis and facilitating oxidative stress, leading to contractile dysfunction. These cytokines collectively promote an adverse cycle of immune activation and myocardial injury, worsening HF symptoms and outcomes [9].

Macrophages and T-cells are key immune cells involved in HF. Macrophages, present in two phenotypes, M1 and M2, play different roles in cardiac function. M1 macrophages are pro-inflammatory and contribute to tissue injury, while M2 macrophages are anti-inflammatory, aiding in tissue repair. In HF, there is often an imbalance favoring M1 macrophages, which perpetuates inflammation and fibrosis. T-cells are similarly dysregulated in HF, contributing to chronic inflammation through prolonged activation and cytokine secretion [10].

Acute and chronic inflammatory responses to heart failure

In heart failure, the inflammatory response can manifest both acutely and chronically. Acute inflammation, often triggered by myocardial infarction or infection, aims to resolve damage but can evolve into chronic inflammation if unresolved. During acute Heart failure exacerbations, inflammatory cytokines, and immune cells are elevated, attempting to repair myocardial tissue [11]. However, in chronic Heart failure, continuous exposure to pro-inflammatory stimuli from cardiac stress leads to long-term immune activation, fibrosis, and stiffening of cardiac tissues, which compromises heart function and accelerates Heart failure progression [12]. Understanding the roles of cytokines like IL-1, IL-6, and TNF-α, along with immune cells such as macrophages and T-cells, provides insight into the critical inflammatory processes that underlie HF. By targeting these pathways, emerging therapies aim to break the cycle of inflammation, offering new hope for improving outcomes in patients with heart failure [13,14].

Rationale for Targeting the Immune System in Heart Failure

In heart failure (HF), immune dysregulation plays a critical role in accelerating disease progression. Under normal circumstances, inflammation helps to repair cardiac injury. However, in HF, chronic immune activation and dysregulation lead to persistent inflammation, which exacerbates cardiac damage. This process involves various immune cells and inflammatory mediators that continuously impair cardiac function, eventually leading to adverse remodeling of the heart muscle and impaired contractility [15]. A significant contributor to inflammation in HF is "sterile inflammation." Unlike infections, which prompt immune responses to pathogens, sterile inflammation occurs in the absence of microbes and is instead triggered by cellular damage and stress. Damaged cardiac cells release molecules known as damage-associated molecular patterns (DAMPs), which interact with immune cells, activating inflammatory pathways. This sterile inflammation in HF drives a cycle of injury and inflammation, further promoting adverse cardiac remodeling and fibrosis [16]. The persistence of inflammatory signals such as cytokines, including IL-1, IL-6, and TNF-α, creates an environment that is damaging to cardiomyocytes and surrounding tissues. These cytokines not only recruit more immune cells to the damaged heart tissue but also enhance oxidative stress and apoptotic pathways. Consequently, a sustained inflammatory state continues to impair heart function over time [17].

Targeting immune pathways in HF represents a novel approach to reduce inflammation and potentially reverse disease progression. By modulating the immune response, therapies can decrease the levels of inflammatory cytokines, reduce immune cell recruitment to cardiac tissue, and mitigate oxidative damage. For instance, immune-modulating drugs that inhibit IL-1 signaling have shown promise in reducing inflammatory markers in HF patients, potentially slowing down the remodeling process. Additionally, emerging therapies that focus on immune cell modulation—such as macrophage polarization or T-cell regulation—are being explored to restore a balanced immune response, aiming to transition the heart from a state of chronic inflammation to a reparative environment [18,19].

Therefore, targeting the immune system in HF addresses a core aspect of the disease's progression by breaking the cycle of sterile inflammation and providing a promising strategy for improving patient outcomes. This approach not only tackles symptoms but also addresses underlying mechanisms of cardiac dysfunction in HF [20].

Current and Emerging Immune-Modulating Therapies in Heart Failure

In heart failure (HF), inflammation and immune responses play crucial roles in disease progression, creating new avenues for treatment. Here's a structured look at various immune-modulating therapies currently being explored in clinical settings and emerging research:

Anti-inflammatory cytokine blockade

IL-1 inhibitors: Interleukin-1 (IL-1), a pro-inflammatory cytokine, contributes significantly to inflammatory cascades in HF. Clinical trials with drugs such as anakinra (an IL-1 receptor antagonist) have shown promise in reducing inflammation. The CANTOS trial, which focused on canakinumab (an IL-1β inhibitor), revealed reductions in inflammation-related cardiovascular events among HF patients, though infection risks were notable [21].

TNF inhibitors: Tumor necrosis factor (TNF) also exacerbates inflammation in HF. However, prior clinical studies on TNF inhibitors like etanercept have yielded mixed outcomes, highlighting the complexity of immune suppression in cardiac contexts, where beneficial effects may be offset by an increased susceptibility to infections [21].

Immune cell modulation

Macrophages and T-cells: Macrophages are central to cardiac inflammation, switching between pro-inflammatory and reparative roles. Strategies to modulate macrophage polarization—shifting them from a damaging (M1) phenotype to a healing (M2) phenotype—are under active investigation. Additionally, certain T-cell subtypes, particularly regulatory T-cells (Tregs), play roles in dampening inflammation and facilitating cardiac repair [22].

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Clinical trials and applications: Emerging research is exploring methods to selectively boost Treg activity in HF patients to help reduce fibrosis and improve recovery. Drugs that modulate T-cell pathways, either directly or through immune checkpoint mechanisms, are being considered as novel therapeutic options [21,22].

Small molecule and antibody therapies

Targeting specific inflammatory mediators: Small molecules targeting cytokine pathways or immune checkpoints (such as PD-1 and CTLA-4 inhibitors) are being developed to manage immune activity without fully suppressing it. Antibody therapies that neutralize inflammatory agents offer targeted intervention, focusing on specific cytokines without broadly suppressing immune function [23].

Examples: Some studies focus on IL-6 and its receptor as potential targets, given IL-6's role in chronic inflammation in HF. Monoclonal antibodies against IL-6 or its receptor, such as tocilizumab, are being explored for their effects on reducing cardiac inflammation while minimizing systemic side effects [24].

Novel targets and future therapies

Chemokine receptor blockade: Chemokine receptors such as CCR2 and CXCR4 are key in recruiting inflammatory cells to cardiac tissue. Blocking these receptors may reduce immune cell infiltration in the heart, limiting damage while promoting healing [25].

Emerging areas: Immune checkpoint inhibitors, traditionally used in cancer therapy, are being tested for their potential to rebalance immune responses in HF. For instance, PD-1/PD-L1 and CTLA-4 pathways, crucial in regulating immune activity, may help modulate inflammation in chronic HF cases [22,26].

With these novel approaches, immune modulation represents a significant advancement in HF therapy, balancing inflammation control with the need for tissue repair and immune defense. As clinical trials progress, these therapies could redefine HF management, potentially improving outcomes by targeting the underlying inflammatory mechanisms central to disease progression [26].

Clinical Implications and Challenges in Immune Modulation for Heart Failure

Immune modulation as a therapeutic strategy for heart failure (HF) holds significant promise but also comes with complex challenges. One primary challenge lies in ensuring treatment safety, as immune-modulating therapies often carry risks of off-target effects. These unintended effects can provoke widespread immune responses, possibly exacerbating HF or inducing other inflammatory conditions. For instance, therapies targeting cytokines like IL-1 and TNF-α, though effective in reducing inflammation, have shown variable impacts on overall HF outcomes due to these off-target reactions and immune system complexities [27].

Another critical aspect is the need for accurate patient stratification to personalize immune-based therapies. HF presents heterogeneously across patients, with different immune profiles and inflammatory responses. Biomarkers such as natriuretic peptides and cardiac troponins, traditionally used for diagnosing HF severity, are being explored for their potential to identify patients who might benefit from specific immune therapies. Advanced biomarkers, like certain cytokine and chemokine levels, could aid in refining patient selection and enhancing treatment efficacy [28]. Further, developing reliable biomarkers for tracking therapeutic efficacy and patient response to immune modulation is essential but challenging. In HF, inflammation's role is complex, and biomarkers must distinguish beneficial from harmful inflammation accurately. This difficulty in biomarker-guided therapy means that ongoing adjustments to treatment may be required, which can be resource-intensive and complicated for healthcare systems to manage effectively [29].

The complexity of the immune system itself also poses a challenge. Heart failure is associated with both innate and adaptive immune system activation and targeting specific pathways may have cascading effects on other immune processes. For example, therapies aimed at macrophage modulation can impact cardiac fibrosis, which is essential in HF management, but also influence immune cells like T-cells, potentially resulting in immune imbalance. Consequently, an in-depth understanding of the HF immune landscape is crucial to refining these therapies [25,29]. Therefore, while immune modulation in HF therapy offers potential, it demands a cautious approach, focusing on safety, precision in patient stratification, and biomarker validation. Future research should aim to refine these strategies to enhance clinical outcomes while minimizing risks [30].

Future Perspectives

The integration of immune-modulatory treatments with existing heart failure (HF) therapies holds great potential for improving patient outcomes. Combining these innovative approaches with traditional therapies such as beta-blockers and ACE inhibitors may enhance the overall effectiveness of HF management by addressing both the hemodynamic and inflammatory aspects of the disease. For instance, studies suggest that beta-blockers can complement immune-modulating strategies by alleviating sympathetic overactivity, a common issue in HF patients, while concurrently reducing inflammation through the modulation of cytokine release.

Moreover, precision medicine could revolutionize the treatment landscape for HF by identifying patients who are most likely to benefit from immune-targeted therapies. Biomarkers that indicate specific inflammatory profiles or genetic predispositions could guide clinicians in selecting the most effective treatment combinations for individual patients. For example, stratifying patients based on their cytokine levels or immune cell compositions could help tailor therapies that specifically address their unique inflammatory pathways. As research progresses, the goal is to establish comprehensive treatment regimens that not only improve clinical outcomes but also optimize the quality of life for HF patients through personalized interventions [31].

This future approach emphasizes a paradigm shift from generalized treatments to individualized care, potentially leading to enhanced therapeutic efficacy and reduced adverse effects. With ongoing advancements in our understanding of

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HF pathophysiology and the immune system's role in disease progression, the integration of precision medicine and combination therapies stands as a promising frontier in heart failure management [32].

Conclusions

So, immune modulation presents a promising frontier in the management of heart failure (HF), with the potential to significantly enhance patient outcomes by addressing underlying inflammatory processes that contribute to disease progression. Current research underscores the intricate relationship between inflammation and HF, highlighting the need for targeted therapies that can modify the immune response without compromising the body's defense mechanisms. Despite the advancements made, further investigations are essential to fully integrate immune-targeted therapies into clinical practice. Future studies should focus on understanding the optimal timing and selection of patients for these therapies, as well as establishing reliable biomarkers that can guide treatment decisions.

The future of HF treatment appears to be leaning towards an immune-focused paradigm, where the interplay between traditional heart failure management strategies and innovative immune-modulating therapies could lead to improved survival rates and quality of life for patients. As research progresses, the concept of personalized medicine will likely become integral in identifying the most suitable candidates for immune therapies, ensuring that treatments are both effective and tailored to individual patient profiles. Ultimately, advancing our understanding of immune mechanisms in HF could pave the way for groundbreaking therapies that transform heart failure management.

Disclosure Statement

No potential conflict of interest was reported by the authors.

References

1. Zhang Y, Bauersachs J, Langer HF. Immune mechanisms in heart failure. Eur J Heart Fail. 2017;19(11):1379-1389. https://doi.org/10.1002/ejhf.942
2. Van Linthout S, Tschöpe C. The quest for antiinflammatory and immunomodulatory strategies in heart failure. Clin Pharmacol Ther. 2019;106(6):1198-1208. https://doi.org/10.1002/cpt.1637
3. Panahi M, Papanikolaou A, Torabi A, Zhang JG, Khan H, Vazir A, et al. Immunomodulatory interventions in myocardial infarction and heart failure: a systematic review of clinical trials and meta-analysis of IL-1 inhibition. Cardiovasc Res. 2018;114(11): 1445-1461. https://doi.org/10.1093/cvr/cvy145
4. Carrillo-Salinas FJ, Ngwenyama N, Anastasiou M, Kaur K, Alcaide P. Heart inflammation: immune cell roles and roads to the heart. Am J Pathol. 2019;189(8):1482-1494. https://doi.org/10.1016/j.ajpath.2019.04.009
5. Boulet J, Sridhar VS, Bouabdallaoui N, Tardif JC, White M. Inflammation in heart failure: pathophysiology and therapeutic strategies. Inflamm Res. 2024;73(5):709-723. https://doi.org/10.1007/s00011-023-01845-6
6. Riehle C, Bauersachs J. Key inflammatory mechanisms underlying heart failure. Herz. 2019;44(2):96-106. https://doi.org/10.1007/s00059-019-4785-8
7. Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know?. Circ Res. 2016;119(1):159-176. https://doi.org/10.1161/CIRCRESAHA.116.308030
8. Wu J, Dong E, Zhang Y, Xiao H. The role of the inflammasome in heart failure. Front Physiol. 2021;12:709703. https://doi.org/10.3389/fphys.2021.709703
9. Li H, Chen C, Wang DW. Inflammatory cytokines, immune cells, and organ interactions in heart failure. Front Physiol. 2021;12:695047. https://doi.org/10.3389/fphys.2021.695047
10. Strassheim D, Dempsey EC, Gerasimovskaya E, Stenmark K, Karoor V. Role of inflammatory cell subtypes in heart failure. J Immunol Res. 2019;2019(1):2164017. https://doi.org/10.1155/2019/2164017
11. Murphy SP, Kakkar R, McCarthy CP, Januzzi Jr JL. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(11):1324-1340. https://doi.org/10.1016/j.jacc.2020.01.014
12. Schumacher SM, Naga Prasad SV. Tumor necrosis factor-α in heart failure: an updated review. Curr Cardiol Rep. 2018;20:1-1. https://doi.org/10.1007/s11886-018-1067-7
13. Reina-Couto M, Pereira-Terra P, Quelhas-Santos J, Silva-Pereira C, Albino-Teixeira A, Sousa T. Inflammation in human heart failure: major mediators and therapeutic targets. Front Physiol. 2021;12:746494. https://doi.org/10.3389/fphys.2021.746494
14. Szabo TM, Frigy A, Nagy EE. Targeting mediators of inflammation in heart failure: a short synthesis of experimental and clinical results. Int J Mol Sci. 2021;22(23):13053. https://doi.org/10.3390/ijms222313053
15. Papamichail A, Kourek C, Briasoulis A, Xanthopoulos A, Tsougos E, Farmakis D, Paraskevaidis I. Targeting Key Inflammatory Mechanisms Underlying Heart Failure: A Comprehensive Review. Int J Mol Sci. 2023;25(1):510. https://doi.org/10.3390/ijms25010510
16. Gullestad L, Ueland T, Vinge LE, Finsen A, Yndestad A, Aukrust P. Inflammatory cytokines in heart failure: mediators and markers. Cardiology. 2012;122(1):23-35. https://doi.org/10.1159/000338166
17. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res. 2015;116(7):1254-1268. https://doi.org/10.1161/CIRCRESAHA.116.302317
18. Sánchez-Trujillo L, Vázquez-Garza E, Castillo EC, García-Rivas G, Torre-Amione G. Role of adaptive immunity in the development and progression of heart failure: new evidence. Arch Med Res. 2017;48(1):1-1. https://doi.org/10.1016/j.arcmed.2016.12.008
19. Lutgens E, Atzler D, Döring Y, Duchene J, Steffens S, Weber C. Immunotherapy for cardiovascular disease. Eur Heart J. 2019; 40(48):3937-3946. https://doi.org/10.1093/eurheartj/ehz283
20. Cocco G, Jerie P, Amiet P, Pandolfi S. Inflammation in heart failure: known knowns and unknown unknowns. Expert Opin Pharmacother. 2017;18(12):1225-1233. https://doi.org/10.1080/14656566.2017.1351948
21. Michels da Silva D, Langer H, Graf T. Inflammatory and molecular pathways in heart failure—ischemia, HFpEF and transthyretin cardiac amyloidosis. Int J Mol Sci. 2019;20(9):2322. https://doi.org/10.3390/ijms20092322
22. Papadimitriou L, P Kalogeropoulos A. Inflammatory biomarkers and therapeutic targets in heart failure. Curr Med Chem. 2015;22(23):2716-2726.
23. Rurik JG, Aghajanian H, Epstein JA. Immune cells and immunotherapy for cardiac injury and repair. Circ Res. 2021;128(11): 1766-1779. https://doi.org/10.1161/CIRCRESAHA.121.318005
24. De Angelis E, Pecoraro M, Rusciano MR, Ciccarelli M, Popolo A. Cross-talk between neurohormonal pathways and the immune system in heart failure: a review of the literature. Int J Mol Sci. 2019;20(7):1698. https://doi.org/10.3390/ijms20071698
25. Sanganalmath SK, Bolli R. Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. Circ Res. 2013;113(6): 810-834. https://doi.org/10.1161/CIRCRESAHA.113.300219
26. Chow SL, Maisel AS, Anand I, Bozkurt B, De Boer RA, Felker GM, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. Circulation. 2017;135(22): e1054-1091. https://doi.org/10.1161/CIR.0000000000000490
27. Wagner KB, Felix SB, Riad A. Innate immune receptors in heart failure: Side effect or potential therapeutic target?. World J Cardiol. 2014;6(8):791. https://doi.org/10.4330/wjc.v6.i8.791

https://doi.org/10.61577/jcri.2024.1000015

28. Ueland T, Gullestad L, Nymo SH, Yndestad A, Aukrust P, Askevold ET. Inflammatory cytokines as biomarkers in heart failure. Clin Chim Acta. 2015;443:71-77. https://doi.org/10.1016/j.cca.2014.09.001
29. Vlachakis PK, Theofilis P, Kachrimanidis I, Giannakopoulos K, Drakopoulou M, Apostolos A, et al. The Role of Inflammasomes in Heart Failure. Int J Mol Sci. 2024;25(10):5372. https://doi.org/10.3390/ijms25105372
30. Sapna FN, Raveena FN, Chandio M, Bai K, Sayyar M, Varrassi G, et al. Advancements in heart failure management: a comprehensive narrative review of emerging therapies. Cureus. 2023;15(10). https://doi.org/10.7759/cureus.46486
31. Nagai T, Nakao M, Anzai T. Risk Stratification Towards Precision Medicine in Heart Failure—Current Progress and Future Perspectives—. Circ J. 2021;85(5):576-583. https://doi.org/10.1253/circj.CJ-20-1299
32. Agarwal M, Pakhare SN. Emerging therapeutic strategies in heart failure management: A narrative review of current evidence and future directions. IJCS. 2024;6(1):32-38. https://doi.org/10.33545/26649020.2024.v6.i1a.47

https://doi.org/10.61577/jcri.2024.1000015