Rituximab as a novel treatment for heart failure: evidence from a case series

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As part of the quest for novel therapies for heart failure (HF) with reduced ejection fraction, inflammation has been considered with interest as a potential target for treatment. Indeed, both myocardial damage and tissue hypoperfusion may induce the production of cytokines that can promote the progression of cardiac dysfunction.1,2 Nonetheless, clinical trials on tumour necrosis factor-α (TNFα) or interleukin-1β (IL-1β) inhibitors have yielded modest or negative results, possibly because the activation of inflammatory pathways is limited and inflammation does not become a crucial disease determinant in the majority of patients.3,4 Conversely, modulation of the immune response is particularly promising in the 30% of cases of myocarditis where inflammation does not resolve and there is a progression to chronic inflammatory dilated cardiomyopathy (DCMi).4 Among 202 patients with DCMi from >6 months, as many as 42% displayed myocardial inflammation on endomyocardial biopsy (EMB).5 Among them, those randomized to steroids and azathioprine developed decrease in left ventricular (LV) volumes, function recovery, and improvement in New York Heart Association (NYHA) class during the first 3 months of treatment. These effects were sustained over 2 years, although no differences in survival were noted.6 Another study evaluated 85 patients with DCMi randomized to prednisone and azathioprine or placebo for 6 months.6 A positive effect of immunosuppression on cardiac remodelling was reported, with a mean LV ejection fraction (LVEF) increase from 26% to 46%; HF symptoms improved as well, and no major adverse effects were found.6 Nonetheless, both steroids and azathioprine have a large spectrum of activity and an unfavourable safety profile, prompting a search for more selective therapeutic approaches.

Rituximab is presently indicated for use in the treatment of non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, antineutrophil cytoplasmic antibody-associated vasculitis including granulomatous with polyangiitis, and microscopic polyangiitis.7 However, it has also been used as a potential off-label treatment option for several other disorders including systemic lupus erythematosus, Sjögren’s syndrome, idiopathic thrombotic purpura, bullous dermatologic diseases, membranous nephropathy, steroid-dependent, or frequently relapsing idiopathic nephrotic syndrome, treatment in recurrent, and de novo glomerular disease after renal transplantation. As a consequence, off-label use of rituximab in these conditions may be limited by cost and accessibility issues in certain countries.

Rituximab targets the CD20 antigen, which is expressed on the surface of mature B lymphocytes, including memory B cells but not on stem cells or plasma cells. Rituximab causes a selective, transient depletion of CD20+ B-cell subpopulations, and represents a more specific and targeted approach to B-cell-driven disorders.7 B-lymphocytes influence and regulate the immune response by several mechanisms and are an important link between the innate and adaptive immune systems. Following a cardiac insult such as a viral infection, the scarce B lymphocytes resident in the heart are activated, and can produce cytokines (TNFα, IL-1β, and IL-6) and chemokines to recruit and activate cells of the innate immunity and T cells, and can also differentiate into plasma cells or memory B cells.8 It has been demonstrated that as many as 53% of patients with DCMi have >7 cells/mm², and 29% have >20 cells/mm².9 Patients with a significant infiltration of CD20+ cells are expected to display a positive response to rituximab.

Tschöpe et al.9 report the results of the first clinical experience with rituximab in six patients with DCMi. Six patients were evaluated, who had systolic dysfunction (LVEF ranging from 14% to 45%) dating from a few months (in two cases) or around 5 years (in the other four cases), >7 CD20+ cells/mm², and no evidence of viral genome on EMB. Two of them had been treated with steroids and azathioprine. Patients received two doses of rituximab (375 mg/m² each, separated by 4 weeks, and together with cortisone 150 mg to avoid
for cardiac complications during and post-administration. Further issues to be solved are the limited access and costs associated with the off-label use of rituximab, particularly in certain countries.

**Lead author biography**

Prof. Michele Emdin is a Professor of Cardiology and a Director of the Cardiovascular Division of the Fondazione Toscana Gabriele Monasterio in Pisa, Italy. His main research interest is circulating biomarkers of heart failure, cardiomyopathies, and the dysregulation of cardiovascular feedback systems as determinants of disease.

**Consent:** This editorial refers to a case series where written patient consent was obtained.

**Conflict of interest:** none declared.

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