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EDITORIAL

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

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This editorial refers to 'Targeting CD20+ B-lymphocytes in inflammatory dilated cardiomyopathy with rituximab improves clinical course: a case series', by C. Tschöpe *et al.*, doi:10.1093/ehjcr/ytz131.

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.[2,3] 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 DCM 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.[5] 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 granulomatosis 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 thrombocytopenic 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/mm^2, and 29% have >20 cells/mm^2.[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/mm^2, 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/m^2 each, separated by 4 weeks, and together with cortisone 150 mg to avoid

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infusion reactions), in addition to standard HF therapy. We may note that the global exposure to rituximab is much lower than in the treatment for haematologic disorders or vasculitis (375 mg/m^2 weekly for up to 8 weeks) or rheumatoid arthritis (1000 mg/m^2 administered two times over 2 weeks). Accordingly, treatment with rituximab was well tolerated by the six patients. Except for one patient with a long disease history and prior immunosuppressive therapy, who remained stable, all patients displayed a response to rituximab, with a meaningful improvement in LVEF, LV end-diastolic diameter, NYHA class, or N-terminal pro-B-type natriuretic peptide. The two patients with a shorter disease history (Patients 1 and 2) displayed the greatest response to rituximab. Interestingly, these patients had also the highest CD20+ cell counts in the baseline EMB (20.25 and 633 cells/mm^2, respectively), and not detectable CD20+ cells in the follow-up EMB; conversely, CD20+ cells were much less represented in patients with a longer disease history (Patients 3–6), including Patient 6, who had 10 cells/mm^2 and did not respond to rituximab, also showing a higher number of CD20+ cells on follow-up biopsy (17.5 cells/mm^2).[9] Patient 6 had also a higher, as well as a significant infiltration of T-lymphocytes and macrophages at baseline. Histological findings in Patient 6 suggested a chronic, longstanding inflammatory process that could not be reversed by rituximab, and could even promote a resistance to B-cell depletion.[10]

Overall, this case series conveys the message that rituximab can be considered in patients with DCMi when the EMB shows a significant infiltrate of CD20+ cells (>7 cells/mm^2) and no evidence of viral infection, particularly when the onset of HF symptoms is recent, but the patient has not responded to conventional therapy. These interesting findings require confirmation in large-scale studies, which should: (i) identify the optimal posology of rituximab in the setting of HF, possibly considering also disease activity, (ii) assess if rituximab therapy may impact on the natural history of the disease, and (iii) search for predictors of response to this drug (possibly including previous treatment with immunosuppressors, disease activity as assessed by inflammatory and cardiac biomarkers, and different composition of the inflammatory infiltrate at the EBM).

Another important issue is the risk of cardiotoxicity related to rituximab therapy. There is emerging data that Rituximab and other monoclonal antibody-based chemotherapy represent a newer class of medications that have cardiotoxic profiles. Rituximab has been reported to cause hypotension, hypoxia, acute myocardial infarction, arrhythmias, and cardiogenic shock during the infusion process. There are also reported incidences where rituximab has caused non-ischaemic dilated cardiomyopathy.[11] While pre-existing cardiovascular disease is not an absolute contraindication to rituximab use, patients being treated with rituximab should be monitored closely 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.

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