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Prognostic Role of Myocarditis-like Episodes and Their Treatment in Patients with Pathogenic Desmoplakin Variants

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Abstract

Background: Inflammatory, myocarditis-like episodes precede and are associated with higher risk of sustained ventricular arrhythmias (VA) and heart failure (HF) in patients with pathogenic/likely pathogenic (P/LP) desmoplakin (DSP) variants. Whether the recurrence and treatment of myocarditis-like episodes influence the outcomes in this population is unknown. This study aimed to assess the prognostic impact of the recurrence and treatment of myocarditis-like episodes in patients with P/LP DSP variants.

Methods: The study was designed as an observational cohort study using all patients with P/LP DSP variants in the DSP-ERADOS Network enrolled at 31 institutions up until April 30th, 2024. Survival from VA and HF endpoints and recurrent myocarditis-like episodes was evaluated for both first and recurrent documented myocarditis-like episodes and the impact of immunosuppressive treatment on outcomes assessed.

Results: A total of 1014 patients with P/LP DSP variants (62.4% female, mean age 40.4±17.4 years, 47.1% probands) were included. Among them, 177 individuals (17.5%) experienced ≥1 documented myocarditis-like episode, with 63 (35.6%) of them receiving immunosuppressive treatment. Immunosuppressive treatment of the first documented myocarditis-like episode was associated with reduced risk of VA and HF outcomes (HR 0.18 [0.07–0.45], p<0.001 and HR 0.09 [0.02–0.39], p=0.001, respectively) over a median follow up of 6.4 [4.0–10.5] years. This risk was comparable to that of patients with no history of myocarditis-like episode, but did not correlate with a reduction in recurrent episodes following completion of initial immunosuppression (HR: 0.85 [0.47–1.54], p=0.599). In contrast, NSAIDs or colchicine treatment did not influence outcomes.

Conclusion: Immunosuppressive treatment of myocarditis-like episodes in DSP patients was associated with improved combined VA/HF outcomes, supporting future prospective evaluation in DSP cohorts.

Keywords

inflammation; myocarditis; arrhythmogenic cardiomyopathy; sudden cardiac death; risk stratification; cardiac arrhythmia; cardiomyopathy; genetics

INTRODUCTION

Desmoplakin (*DSP*) cardiomyopathy recently emerged as a distinct form of heritable cardiomyopathy with frequent predominantly left-ventricular (LV) or biventricular involvement and high burden of potentially lethal ventricular arrhythmias (VA)^{1–5}. Up to 30% of patients with pathogenic (P) or likely pathogenic (LP) *DSP* variants in reported study cohorts are known to experience inflammatory myocarditis-like episodes, characterized by sudden chest pain, cardiac inflammation, non-coronary artery disease (CAD) related increases of cardiac troponins in the absence of viral triggers^{1,5,6}.

Overall, the occurrence of these myocarditis-like episodes in *DSP* variant carriers has been strongly associated with fibrosis in the left ventricle (LV), as around 90% of cases have demonstrated presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR), even in patients with a normal left ventricular ejection fraction (LVEF)^{1,2}. Moreover, recent data indicated that these events represent a significant clinical occurrence in the natural history of *DSP* cardiomyopathy, as they are followed by an almost three-fold increased risk of VA and nearly five-fold elevated risk of heart failure (HF) hospitalization in this population^{2,5}.

These observations have prompted consideration of inflammation as a therapeutic target in *DSP* cardiomyopathy patients, particularly those presenting with myocarditis. However, it remains unknown whether treating myocarditis-like episodes alters outcomes in the *DSP* population. To address this knowledge gap, we leveraged the data from the *DSP*-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) Network, a large international and multicenter cohort of patients with core lab-adjudicated P/LP *DSP* variants, to characterize the impact of treatment of myocarditis-like episodes on combined VA/HF outcomes and recurrent myocarditis-like episodes.

METHODS

Study population

The entire patient cohort enrolled in the *DSP*-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) Network was used for this study (n=1014 patients). The *DSP*-ERADOS Network has been described before⁷. In brief, it is an international collaboration currently including 31 institutions across 9 countries (United States, Canada, Italy, United Kingdom, the Netherlands, France, Germany, Spain and Australia), with each institution functioning as an independent, prospective, observational patient registry obtaining regulatory approval and patient consent according to individual institution regulations. Individuals seen at these institutions by April 30th, 2024 were entered in the *DSP*-ERADOS registry if they carried a P/LP variant in the *DSP* gene, as defined by the American College of Medical Genetics and Genomics (ACMGG)⁸, after core-lab centralized assessment by two specialists in ACM cardiac genetics (B.M. and C.A.J). The whole cohort was divided into two sub-cohorts, according to the occurrence (DSPMyo+, n=177) or non-occurrence (DSPMyo-, n=837) of myocarditis-like episodes at any point of their clinical history. The data supporting this manuscript is available upon reasonable request to the corresponding author. This manuscript adheres to the STROBE reporting guidelines.

Data Collection

The data collection strategy for patients enrolled in the *DSP-ERADOS* Network has been described before⁵. In brief, demographics, patient medical history, genetic test results, and cardiac diagnostic testing (12-lead electrocardiogram (ECG), echocardiography, cardiac magnetic resonance (CMR), 24 h Holter ECG monitoring) were retrieved for each patient by each involved institution at the time of first clinical assessment (defined as patient baseline). Outcomes were adjudicated locally at each participating center via review of ECG, implantable cardioverter-defibrillator (ICD) interrogations, and patient medical records. Probands were defined as the first affected individual in a family who came to medical attention. Additionally, for each myocarditis-like episode, available data regarding clinical presentation, diagnostic tests performed, and therapeutic options employed at that time were collected.

Definitions and Outcomes

Myocarditis-like episodes were defined in accordance to prior desmosomal and DSP-specific literature on the topic^{6,9}, upon the presence of increased levels of serum cardiac troponin (>99th percentile) during the index event after exclusion of CAD etiology and a combination of histologic or CMR criteria consistent with acute myocarditis (classic or updated Lake Louise Criteria or presence of epicardial LGE pattern)^{10,11}. DSP regions were classified as constitutive non-mediated decay (NMD) competent, non-constitutive NMD competent, or constitutive NMD incompetent, as per prior literature¹². Sustained VA occurrence was defined as the combination of occurrence of an episode of sustained ventricular tachycardia episode ≥ 30 seconds at ≥ 100 b.p.m. or with hemodynamic compromise, ventricular fibrillation/flutter (VF), sudden cardiac arrest (SCD) or appropriate ICD interventions for a sustained VA, in line with prior work from the *DSP-ERADOS* Network^{4,5,7}. Myocarditis-like episodes were classified as treated with immunosuppression if a patient received a medication interfering with the innate or acquire immune system (namely, for the purpose of this study, a medication being part of one of the following groups: corticosteroids, calcineurin inhibitors, mammalian target of rapamycin inhibitors, antimetabolites, intravenous immunoglobulins (IVIG), or an interleukin-1 receptor antagonist). The DSP Risk Score was calculated for qualifying patients (*DSP* variant carriers without prior episodes of VA)⁷, using the last version of the risk calculator available online at the website www.dsp-risk.com.

The main aim of the study was to assess the impact of myocarditis-like episodes (single and recurrent) on patient outcomes (both as a combination of VA episodes and HF hospitalization and as individual outcomes) as well as to assess the impact of treatment of myocarditis-like episodes with a) immunosuppressive medications; b) non-steroidal anti-inflammatory drugs (NSAIDs); and c) colchicine on long term patient outcomes (both as a combination of VA episodes, HF Hospitalization and recurrent myocarditis, and as individual outcomes).

Statistical Analysis

Nominal variables were expressed as number (%), and continuous variables as mean $\pm$ standard deviation (s.d) or median (interquartile range [IQR]), as appropriate.

Comparisons for binary variables were performed by Chi-square or Fisher's exact tests. For continuous variables, independent t-tests or Mann-Whitney U tests were used.

First, we aimed to assess the risk of repeat myocarditis compared to one myocardial episode or no myocardial episode. To do so, we used multi-state modelling which adjusted treatment usage at time of the respective myocardial episode. In this model, we determined no myocarditis-like episode, first episode, repeat episode, and a composite of VA and HF as separate states from which an individual can transition to a more severe disease state. Transitioning to a less severe disease state (e.g. from repeat myocarditis-like episode to first episode) was considered impossible as per previous studies^{13,14}, and all states were modeled as time-stamped events. For a visual representation on how a P/LP DSP variant carrier could progress see Figure S1. An in-depth description of the type of Markov Chain, and the assumptions and restrictions of the model is provided in the Supplemental Methods.

Second, to visualize the overall probability of survival free from the endpoints (i.e. VA episodes, HF hospitalizations, new myocarditis episodes, and a combination of them) we used Kaplan-Meier curves and compared groups using the log-rank test. As a sensitivity effort, we also performed the above-mentioned Kaplan-Meier curves considering (1) colchicine and NSAID treatment as separate groups; and (2) the effect of treatment at the time of their second myocarditis-like episode. The initiation of treatment for the primary endpoints (VA episodes, HF hospitalizations, new myocarditis episodes) were tested by Cox proportional hazard regression, and hazard ratios (HR) were reported with 95% confidence intervals (CI). The proportional hazard's assumption was checked for each predictor using Schoenfeld residuals. The event rates for the primary endpoints, including the 95% CI, were calculated using the Kaplan-Meier method. Of note, since there was no statistical difference between the *DSP*Myo+ treated with immunosuppression and those not treated with immunosuppression (Table 1), we did not have to perform statistical analyses to adjust for baseline differences between groups (e.g. propensity score matching)

Last, utilizing the remaining P/LP *DSP* cohort from the *DSP*-ERADOS Network who did not have a myocarditis-like episode (*DSP*Myo-), we determined the added risk of treated myocarditis-like episode on the risk of VA and/or HF hospitalization at the time of first episode compared to the *DSP*Myo- cohort using time-dependent Kaplan Meier curves. Time zero for all groups was set as the time of first clinical presentation for *DSP* ACM for all groups. No missing data was imputed. A p-value<0.05 was considered statistically significant. Data was analyzed using R version 4.1.2 (Boston, MA, USA), including the survival, survminer and msm package. The R code will be made available upon reasonable request to the corresponding author.

RESULTS

Patient Population & Baseline

Of the entire 1014 patients in the *DSP*-ERADOS Network, 177 patients were included in the *DSP*Myo+ cohort. Their baseline characteristics, alongside patients in the *DSP*Myo- cohort, are reported in Table1. *DSP*Myo+ patients were young (mean age 34.6±15.5 years old), and frequently female (n=106, 59.9%) and probands (n=122, 68.9%). For 107 (60.5%) patients,

a myocarditis-like episode represented the first clinical presentation, with 57 (32.2%) patients experiencing multiple myocarditis-like episodes over time. Most patients (n=140, 79.1%) harbored truncating *DSP* variants.

At baseline, around half of the *DSP*Myo+ experienced palpitations (n=83, 46.9%), a third had dyspnea (n=66, 37.9%) and/or NSVT (n=64, 36.2%), and median PVC burden was 1055 [262–2405]/24h. Baseline CMR was available in 152 (85.9%) patients (LVEF% 51.7±10.4; LVEF<35 in 7.5%; RVEF% 52.2±10.1; LGE present in n=132, 86.8%).

Myocarditis Episodes

The 177 *DSP*Myo+ patients experienced a total of 290 individual myocarditis-like episodes (median/patient 1 [1–2]) over a median follow up of 6.4 [4.0–10.5] years). At the time of first myocarditis-like episode, a CMR was available in 154 (87.0%) patients. LV and RV systolic function at this time was mostly normal (LVEF 51.6±10.3% and RVEF 52.2±10.1%) and LGE was almost always present (140/154, 90.9%), involving multiple cardiac segments (median 4 [2–6]). A pericardial effusion was present in 23/154 (14.9%) patients. Table S1 reports ECG data at the time of first myocarditis-like episode.

In those *DSP*Myo+ patients for which a myocarditis-like episode was not the first clinical presentation and for which a CMR was available both at baseline and at the time of first episode, no significant changes in LVEF or RVEF were observed (50.6±11.9 vs 46.5±12.8%, p=0.790; 50.4±8.6 vs 48.4±11.7%, p=0.181) but a significant interval increase in the amount of LGE was present (median n of segments with LGE: 4 [2–6] vs 5 [4–7], p<0.001).

As Table2 shows, 63 (35.6%) patients received immunosuppressive medications for at least one of their myocarditis-like episodes. A total of 106/290 (36.6%) episodes were treated with immunosuppressive medications, most commonly using a corticosteroid (n=95/106). Of these, 64 episodes were treated with a corticosteroid only regimen while 31 were treated with a corticosteroid plus an additional immunosuppressive medication (Table2). The first myocarditis-like episode was treated with immunosuppressive medications in 56 (31.6%) patients and with NSAIDs/colchicine in 32 (18.1%) patients, while 89 (50.3%) patients were not treated with immunosuppression or NSAIDs/colchicine. The characteristics of patients receiving and not receiving immunosuppression were overall similar (TableS2), except for a significantly higher presence of LGE (96.5% vs 81.1%, p=0.006) and trends towards a larger extent of LGE (median segment 4 [3–7] vs 4 [1–6]; p=0.057) in patients receiving immunosuppression.

Follow Up and Long-Term Outcomes

Over a follow up of 6.4 [4.0–10.5] years, in the *DSP*Myo+ cohort 69 (39.0%) patients experienced an arrhythmic event, and 34 (19.2%) patients had a HF hospitalization, with a median 1.4 [0.12–4.8] years from myocarditis-like episode to adverse outcome. Compared to *DSP*Myo- patients, both VA (6.2 [4.9–7.9] vs 4.0 [3.4–4.7]%/year; p=0.009) and HF hospitalization (3.4 [2.5–4.6] vs 1.7 [1.3–2.1]%/year; p=0.003) yearly rates were significantly higher in the *DSP*Myo+ cohort. Complete follow up data for the *DSP*Myo+ cohort and for the *DSP*Myo- cohort are reported in Table3 and TableS3. As reported in Figure1, a progressive increase in overall VA or HF risk was associated with the occurrence

of multiple myocarditis-like episodes in the cohort (HR for single myocarditis-like episode: 1.94 [1.38–2.71]; $p=0.001$; HR for multiple myocarditis-like episodes: 4.49 [1.33–4.05]; $p=0.003$) (Calibration curves are reported in FigureS2).

Overall rates of VA, HF hospitalizations, repeat myocarditis-like episodes, and a combination of the three, according to treatment received at the time of first myocarditis-like episode are shown in Figure2. *DSP*Myo+ patients whose first myocarditis-like episode was treated with immunosuppressive medications, when compared to untreated patients or patients being treated with NSAIDs/colchicine, had significantly lower rates of VA (1.8 [0.1–3.4] vs 8.3 [5.7–10.5] vs 11.0 [5.7–14.8]/year; $p<0.001$; HR for use of immunosuppression: 0.18 [0.07–0.45], $p<0.001$; HR for use of NSAIDs/colchicine: 1.51 [0.88–2.60], $p=0.138$) and HF hospitalizations (0.7 [0.1–1.7] vs 5.5 [3.1–7.4] vs 3.5 [0.4–6.0]/year, $p<0.001$; HR for use of immunosuppression: 0.09 [0.02–0.39], $p=0.001$; HR for use of NSAIDs/Colchicine: 0.59 [0.27–1.29], $p=0.187$). No differences in rates of new myocarditis-like episodes (6.0 [3.2–8.3] vs 7.2 [4.8–9.1] vs 10.0 [4.5–14.0]/year, $p=0.700$; HR for immunosuppression 0.85 [0.47–1.54], $p=0.599$; HR for NSAIDs/colchicine: 1.16 [0.60–2.22], $p=0.662$) were observed across the groups receiving different treatments (FigureS3 and Table S4). The observed benefit of immunosuppression on VA and HF hospitalizations was also observed when performing the same analysis from the timepoint of the second myocarditis-like episode in those with multiple episodes (Figure S4 and Table S5). Finally, the time-dependent risk profile of *DSP*Myo+ receiving immunosuppression was better than *DSP*Myo- for VA events (HR compared to *DSP*Myo-: 0.40 (0.17–0.99); $p=0.047$) and similar for HF hospitalizations (HR compared to *DSP*Myo-: 0.15–1.56; $p=0.226$) (Figure3).

DISCUSSION

Leveraging a large international multicenter cohort of 1014 patients with P/LP *DSP* variants from the *DSP*-ERADOS network, we assessed the characteristics and clinical consequences of myocarditis-like episodes – a key feature in *DSP* cardiomyopathy – along with the impact of their treatment on combined incident VA/HF outcomes and recurrent myocarditis-like episodes. Our findings indicate that almost 1 in 5 patients with P/LP *DSP* variants experienced clinical myocarditis, and among them, 1 in 3 received immunosuppressive treatment. Immunosuppressive treatment of myocarditis-like episodes (initial or repeat presentations) was associated with substantially lower risk for VA and HF outcomes, as compared to patients with no treatment. Interestingly, however, immunosuppressive treatment did not have an impact on recurrence of myocarditis-like episodes, suggesting that immunosuppression may mitigate consequences of myocarditis without altering the fundamental cause of these episodes. Finally, the future VA/HF risk of patients following immunosuppressive treatment at the time of myocarditis was found to be similar than the one of patients harboring *DSP* variants that never experienced myocarditis-like episodes (*DSP*Myo- cohort). These novel insights shed light on critical aspects of the natural history of *DSP* cardiomyopathy and suggest a possible avenue for mitigating adverse events in the subpopulation developing myocardial injury episodes.

Myocarditis-like episodes and impact on clinical outcomes

Over the past few years, the reported prevalence of myocarditis-like episodes in patients harboring variants in the *DSP* gene has led to incorporation of this unique phenotypic feature into the emerging entity of *DSP* cardiomyopathy^{1,15}. The impact of these myocarditis-like episodes on clinical outcomes, however, is poorly understood and has in turn garnered much attention in the field.

Initially, upon occurrence of myocarditis-like episodes, a study from *Wang* et al observed a 2.5x and a 7.5x increase in the risk of VA and HF, respectively, in a single center cohort of 91 individuals with *DSP*P/LP variants, with its significance persisting even after multivariate adjustment². A subsequent study from the *DSP*-ERADOS Network confirmed these associations in a larger international cohort, revealing a more than 2-fold increased risk for VA and a 5-fold increased risk for HF endpoints in patients with *DSP* variants after the occurrence of a myocarditis-like episode⁵. The strength of the link between myocarditis-like episodes and these outcomes was even further highlighted by the progressive worsening outcomes observed with recurrent myocarditis-like episodes in the current study (as per Figure1).

Interestingly, the currently available evidence shows that most adverse outcomes in *DSP*Myo+ patients occur well after resolution of the myocarditis like-episode acute phase. In several case series and cohort studies, myocarditis is frequently reported as the presenting symptoms for patients with *DSP* variants^{3,15,16}, while *Wang* et al reported myocarditis-like episodes (median age: 28 years) occurring several years prior to VA (median age: 33 years) or HF (median age: 38 years) events². Similar to that experience and to the previous report from the *DSP*-ERADOS Network (reporting a median time to VA after myocarditis-like episode of 0.7 [0.5–4.6] years), this current study showed a delay between the occurrence of the myocarditis-like episode and subsequent adverse outcomes of 1.4 [0.12–4.8] years. This time course seems to speak against an increased risk due to the immediate impact of cardiac inflammation. Instead, it seems reasonable to postulate that, as in non-*DSP* populations¹⁷, these myocarditis-like episodes facilitate the development of myocardial fibrosis that in turn creates an arrhythmogenic milieu and impaired contractility, which persists even after the inflammatory myocardial damage is healed¹⁸. Indeed, the concept that myocarditis-like episodes may exacerbate fibrosis is supported by the high rate of LGE presence on CMR reported in patients with *DSP* variants and prior/current myocarditis-like episodes (*Wang* et al: 94%; *Smith* et al: 90%; 90.9% in the current study), as well by the increase in the extent of cardiac fibrosis as observed in this study.

Impact of treatment of myocarditis-like episodes on clinical outcomes

This study represents the first large report assessing the impact of immunosuppressive therapy in patients with *DSP* variants and myocarditis-like episodes. While anecdotal observations from case reports have reported potential benefit of immunosuppression^{16,19–22}, a lack of systematic evaluation in a large cohort has left a large knowledge gap in the clinical management of these patients. In our multicenter cohort, 31.6% of patients with myocarditis-like episodes received immunosuppressive treatment for the first myocarditis-

like episode, with NSAIDs or colchicine instead prescribed in 18.1%. The remaining half (50.3%) of the cohort did not receive treatment at that time.

In our study, patients with P/LP *DSP* variants experiencing a myocarditis-like episode were less likely to develop either VA or HF endpoints if they received immunosuppressive treatment, while there was no apparent effect associated with the use of NSAIDs or colchicine. The risk of adverse cardiac outcomes in patients with myocarditis episodes who were treated with immunosuppression was similar to patients with no history of myocarditis episodes, appearing de-facto to negate the otherwise expected worsening of risk in patients experiencing myocarditis episodes. Notably, the risk of VA in the cohort treated with immunosuppression was numerically lower than of those in the *DSP*Myo- cohort. Although limited by retrospective analysis and sample size, we speculate that chronic, sub-clinical inflammation episodes in the *DSP*Myo- cohort could potentially drive the natural history of those patients. This concept has been previously postulated^{18,23,24}, and potentially supports studies of chronic (rather than acute episodic) immunosuppression, as suggested by preliminary reports on DSP and other genetic cardiomyopathies with biopsy-proven myocarditis²⁵. For example, in the randomized controlled Tailored Immunosuppression in virus-negative Inflammatory Cardiomyopathy (TIMIC) trial²⁶, genetically undifferentiated patients with biopsy-proven, virus-negative chronic myocarditis were randomized to immunosuppressive therapy (prednisone + azathioprine for 6 months) or placebo. Treatment with immunosuppression resulted in lower incidence of heart transplant and cardiovascular mortality at a 20 year follow-up²⁷. Interestingly, in the TIMIC trial and our study, no impact of immunosuppression on the occurrence of recurrent myocarditis episodes was observed, although recurrent episodes of myocarditis appeared to clinically respond in both studies to repeat immunosuppression treatment²⁷. Although it is unclear what portion of the TIMIC cohort carried *DSP* variants, the similarities of presentation and treatment response observed also in our cohort may provide additional support to consider immunosuppressive treatment in DSP patients presenting with myocarditis.

Strikingly, we found that immunosuppression did not result in a reduction of future myocarditis-like episodes. This finding is in line with what was observed in many of the previous case reports and small case series, where patients harboring DSP variants have been reported to experience multiple episodes of breakthrough myocarditis even when on continuous immunosuppression^{16,20,21}. This observation indicates that immunosuppression may not treat the fundamental driver of disease in *DSP* cardiomyopathy, which is likely a pro-inflammatory genetic background that persists despite treatment of acute inflammation²⁸, further emphasizing the need for continued efforts to develop targeted gene therapies for inherited cardiomyopathies.

Limitations and Future Perspectives

This is the largest study investigating the frequency and prognostic impact of myocarditis-like episodes and their respective treatment in the *DSP* population. Nonetheless, the findings of this study should be interpreted considering several limitations. First, referral bias affects our ability to accurately assess the true prevalence of myocarditis-like episodes in the *DSP* population. Additionally, as myocarditis-like episodes are primarily investigated upon

a symptomatic patient presentation, the possibility of under-reporting of asymptomatic / pauci-symptomatic myocarditis episode should be acknowledged. Future prospective natural history studies will be needed to fully elucidate the true prevalence of these episodes. Second, due to the retrospective study design, the decisions regarding myocarditis-like episode work-up and therapy, including indications, specific agents, dosage and duration, were exclusively within the discretion of the managing clinician and institutional practices. Accordingly, the effectiveness of individual management protocols could not be properly evaluated in our cohort and a center-level regional bias could not be completely excluded. Additionally, future investigations will need to consider potential immunosuppression related adverse events such as corticosteroid related hyperglycemia and rates of infection when weighing the risk-benefit of immunosuppression on cardiac endpoints.

While our findings are exploratory, they clearly confirm the adverse prognostic impact of myocarditis-like episodes and suggest a potential benefit of immunosuppressive treatment for myocarditis-like episodes in reducing VA/HF outcomes in the *DSP* population. These data therefore are hypothesis generating and should prompt corroboration through prospective study, including randomized controlled clinical trials designed to answer whether immunosuppressive interventions for patients with myocarditis-like episodes can alter the trajectory of DSP cardiomyopathy.

Conclusions

Patients with P/LP *DSP* variants who experience episodes of inflammatory myocardial injury face a markedly elevated risk of VA, HF, and recurrent myocardial injury. Our analysis suggests that the risk associated with the combined endpoint of VA and HF in this cohort could potentially be mitigated through immunosuppressive treatment for both initial episodes and subsequent recurrences of myocardial injury, while the treatment does not affect the risk of recurrent myocarditis-like episodes. Given that the inflammatory process is a potential precursor to myocardial fibrosis and ventricular dysfunction, our findings support the therapeutic potential of targeting inflammatory signaling pathways in individuals with *DSP* cardiomyopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective

1) What is new?

- Patients carrying pathogenic / likely pathogenic variants in the desmoplakin gene are prone to frequent myocarditis-like episodes
- The occurrence of these episodes is associated with a subsequent increase in the risk of ventricular arrhythmias and heart failure episodes in a dose dependent fashion (more myocarditis-like episodes = higher risk)
- The use of immunosuppressive medications at the time of myocarditis-like episodes was associated with a significant reduction in the risk of subsequent adverse events

2) What are the clinical implications?

- This retrospective analysis suggests a potential mitigating role of immunosuppressive treatment at the time of myocarditis-like events on VA and HF occurrence in patients with DSP variants;
- This data strongly supports future randomized controlled trials in the space of immunosuppression for patients with DSP variants

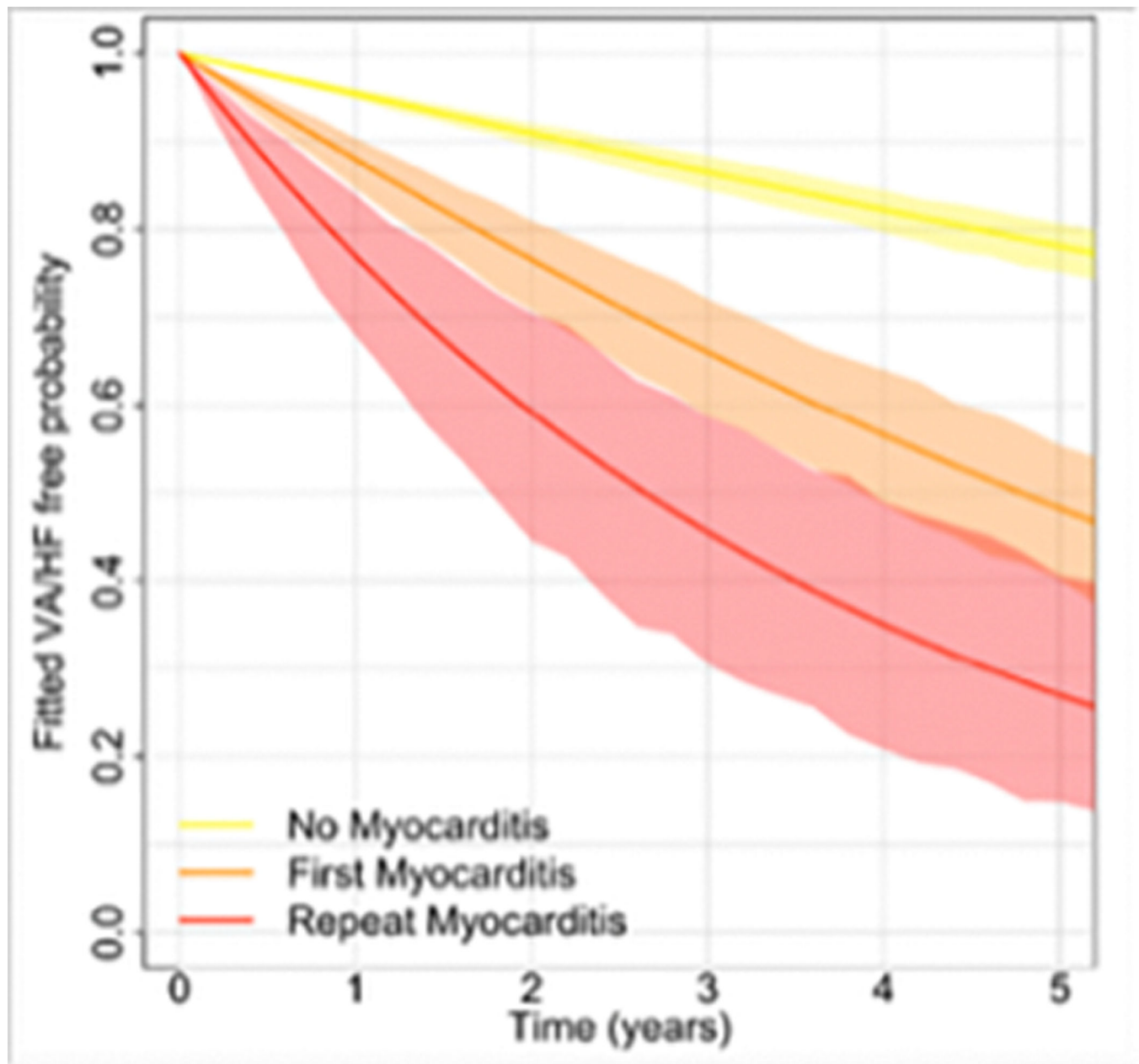


Figure 1. Risk profile of patients harboring DSP variants according to myocarditis-like episodes occurrence

Survival curve of occurrence of VA or HF in patients with *DSP* P/LP variants without a myocarditis-like episode (yellow line), one myocarditis-like episode (orange line) and repeat myocarditis-like episodes (red line). The fitted probabilities are obtained from the Markov Chain described, visualized, and calibrated in the Supplemental methods, Figure S1, and Figure S2, respectively. Shaded areas indicate 95% CI. DSP: desmoplakin; HF: heart failure; P/LP: pathogenic/likely pathogenic; VA: ventricular arrhythmias.

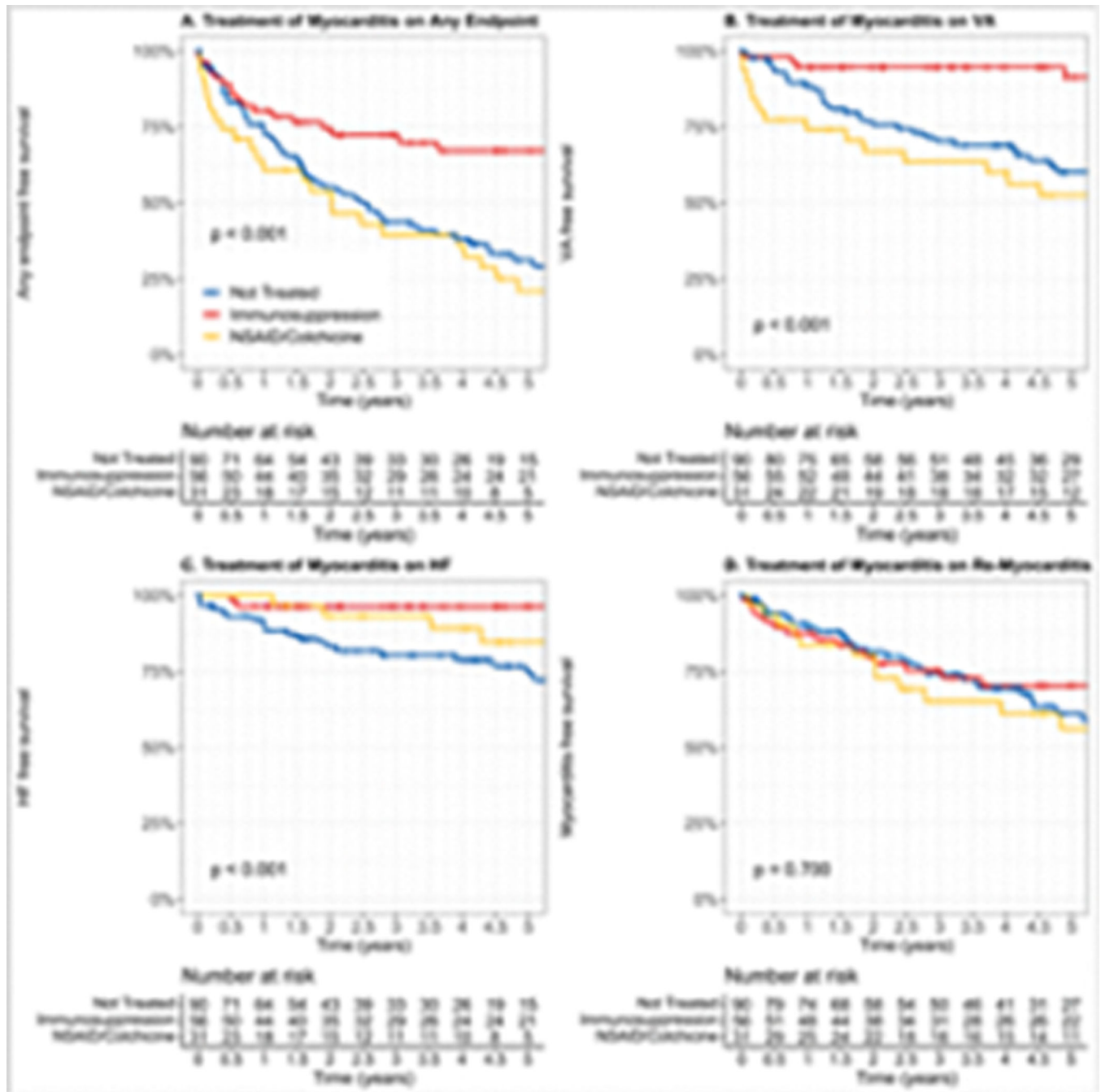


Figure 2 – DSPMyo+ outcomes based on treatment of first myocarditis-like episode

Survival curve of occurrence of any endpoint (i.e. repeat myocarditis-like episode, VA, or HF episode) (panel A), VA (panel B), HF (panel C), and repeat myocarditis-like episode (panel D) in patients not treated (blue line), treated with immunosuppressives (red line), or treated with NSAIDs/colchicine (yellow line).

The p-values are calculated using the log-rank test. Significant pairwise comparisons were: (1) immunosuppression vs not treated for any endpoint ($p < 0.001$), VA ($p < 0.001$), and HF hospitalization ($p < 0.001$) and (2) immunosuppression vs NSAID/Colchicine for any

endpoint ($p<0.001$), VA ($p<0.001$), and HF hospitalization ($p<0.008$). NSAIDs/Colchicine vs not treated did not have any significant difference for any endpoint comparison. HF: heart failure; NSAID: non-steroidal anti-inflammatory drugs; VA: ventricular arrhythmias

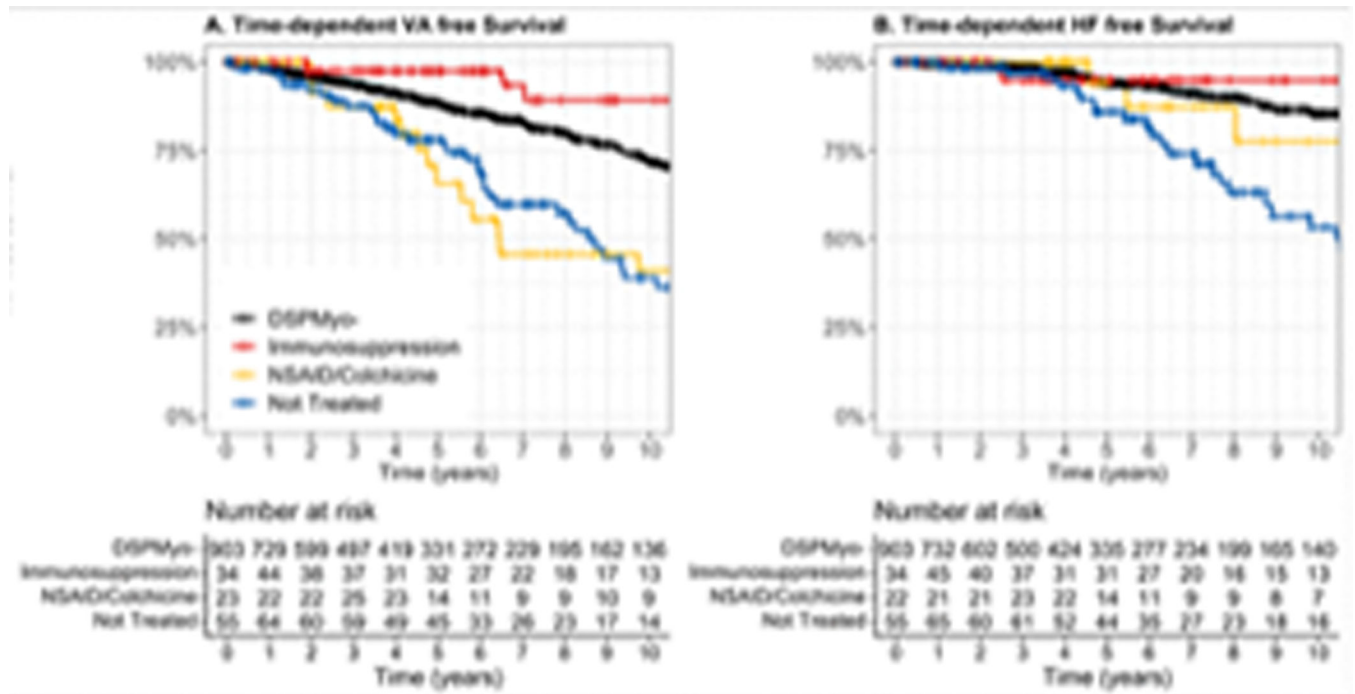


Figure 3 –. comparison of different risks profiles of patients harboring DSP variants depending on occurrence of myocarditis-like episodes and treatment received at the time of myocarditis-like episode

Time-dependent Kaplan Meier Curves for the occurrence of VA (panel A) and HF (panel B) in patients without a myocarditis-like episode (black line; *DSPMyo-*), with a first myocarditis-like episode not treated (blue line), with a first myocarditis-like episode treated with immunosuppression (red line), or with a first myocarditis-like episode treated with NSAID/colchicine (yellow line). The number at risk vary at the variation of the patient status during follow up.

HF: heart failure; NSAID: non-steroidal anti-inflammatory drug; VA: ventricular arrhythmias;

Table 1
Baseline characteristics of the *DSP*Myo-, *DSP*Myo+, and *DSP*Myo+ receiving immunosuppression cohorts

Cohort Characteristics at Baseline					
	<i>DSP</i> Myo- (n=837)	<i>DSP</i> Myo+ (n=177)	P value vs <i>DSP</i> Myo-	<i>DSP</i> Myo+ receiving immunosuppression (n=63)	P value vs <i>DSP</i> Myo-
Age at baseline, mean±s.d.	41.6±17.6	34.6±15.5	<0.001	33.1±16.5	<0.001
Male sex, n (%)	310 (37.0)	71 (40.1)	0.443	31 (49.2)	0.054
Probands, n (%)	356 (42.5)	122 (68.9)	0.433	45 (71.4)	<0.001
Ethnicity, n(%)					
White/Caucasian, n (%)	781 (93.3)	166 (93.8)	0.817	59 (93.7)	0.917
Hispanic, n (%)	16 (1.9)	3 (1.7)	1.000	0	0.620
African-American/Black, n (%)	14 (1.7)	2 (1.1)	1.000	1 (1.6)	1.000
South Asian, n (%)	16 (1.9)	6 (3.4)	0.2220	3 (4.8)	0.142
East Asian, n (%)	8 (1.0)	0	0.363	0	1.000
Middle Eastern, n (%)	2 (0.2)	0	1.000	0	1.000
Palpitations at baseline, n (%)	274 (32.7)	83 (46.9)	<0.001	26 (41.3)	0.166
Dyspnea at baseline, n (%)	166 (19.8)	66 (37.3)	<0.001	16 (25.4)	0.289
NYHA I, n (%)	15 (9.0)	9 (13.6)	0.229	2 (12.5)	0.437
NYHA II, n (%)	103 (62.1)	45 (68.2)	0.381	13 (81.3)	0.057
NYHA III/IV, n (%)	48 (28.9)	12 (18.1)	0.092	1 (6.3)	0.162
<i>DSP</i> variant type					
Truncation, n (%)	681 (81.4)	140 (79.1)	0.485	50 (79.4)	0.696
Splice site, n (%)	89 (10.6)	14 (7.9)	0.276	6 (9.5)	0.782
Missense, n (%)	67 (8.0)	23 (13.0)	0.033	7 (11.1)	0.387
Variant region (n 768/151/55)*, n(%)					
Constitutive NMD competent	436 (56.8)	78 (51.7)	0.141	23 (41.8)	0.031
Non-constitutive NMD competent	152 (19.8)	38 (25.2)	0.136	15 (27.3)	0.183
Constitutive NMD incompetent	180 (23.4)	35 (23.2)	0.945	17 (30.9)	0.210
Dermatological features, n (%)	177 (21.2)	30 (17.0)	0.208	8 (12.7)	0.145
History of NSVT at baseline, n (%)	143 (17.1)	64 (36.2)	<0.001	21 (33.3)	<0.001
History of HF, n (%)	70 (8.4)	18 (10.2)	0.438	4 (6.4)	0.574
History of syncope, n (%)	80 (9.6)	26 (14.7)	0.043	8 (12.7)	0.418
Sustained VA at/prior to baseline, n (%)	107 (12.8)	20 (11.3)	0.588	6 (9.5)	0.415
PVC burden at baseline, median [IQR]	606 [20–2540]	1055 [262–2405]	0.012	780 [224–2333]	0.182
Echo data at baseline (n=727/173/60)					
LVEF (%), mean±s.d.	50.1±13.9	50.3±13.0	0.850	52.3±11.0	0.232
Moderate to severe RV dysfunction, n (%)	34 (4.7)	4 (2.3)	0.208	0	0.103
LVWMA, n (%)	139 (19.1)	60 (34.7)	<0.001	21 (35.0)	<0.001

Cohort Characteristics at Baseline					
	DSPMyo- (n=837)	DSPMyo+ (n=177)	P value vs DSPMyo-	DSPMyo+ receiving immunosuppression (n=63)	P value vs DSPMyo-
RVWMA, n (%)	74 (10.2)	14 (8.1)	0.406	3 (5.0)	0.264
CMR data at baseline (n=571/152/57)					
LVEF (%), mean±s.d.	50.5±12.4	51.7±10.4	0.302	52.4±9.6	0.262
LVWMA, n (%)	142 (24.8)	59 (38.8)	0.001	26 (45.6)	<0.001
LVEDVi, median [IQR]	87.2 [73.0–107.0]	87.0 [76.2–101.0]	0.534	86 [75–101]	0.383
RVEF (%), mean±s.d.	52.1±10.7	52.2±10.1	0.950	52.7±9.6	0.684
RVWMA, n (%)	110 (19.2)	22 (14.5)	0.177	8 (14.0)	0.919
RVEDVi, median [IQR]	80.0 [68.1–99.0]	80.2 [70.3–98.0]	0.977	80 [66–99]	0.707
Presence of LGE, n (%)	365 (59.8)	132 (86.8)	<0.001	55 (96.5)	<0.001
Phenotype fulfilled, n (%)					
Right-dominant form, n (%)	30 (3.6)	2 (1.1)	0.100	0	0.261
Biventricular form, n (%)	123 (14.7)	29 (16.4)	0.567	9 (14.3)	0.929
Left dominant formn (%),	404 (48.3)	109 (61.6)	0.001	41 (65.1)	0.010
Therapy at baseline					
BB, n (%)	379 (45.3)	127 (71.8)	<0.001	44 (69.8)	0.002
AAD, n (%)	96 (11.5)	30 (17.0)	0.044	12 (19.1)	0.074
Ace-i/ARB, n (%)	276 (33.0)	89 (50.3)	<0.001	32 (50.8)	0.004
MRA, n (%)	90 (10.8)	28 (15.8)	0.056	5 (7.9)	0.483

AAD: anti-arrhythmic drugs; ARB: angiotensin receptor blocker; BB: beta-blockers; DSP: desmoplakin; HF: heart failure; ICD: implantable cardioverter defibrillator; LGE: late gadolinium enhancement; LVEDVi: left ventricular end diastolic volume indexed; LVEF: left ventricular ejection fraction; LVWMA: left ventricular wall motion abnormalities; MRA: mineralocorticoid receptor antagonist; NMD: non-sense mediated decay; NSVT: non-sustained ventricular tachycardia; NYHA: New York Heart Association; PVC: premature ventricular complexes; RVEDVi: right ventricular end diastolic volume indexed; RVEF: right ventricular ejection fraction; RVWMA: right ventricular wall motion abnormalities; VA: ventricular arrhythmia. Phenotypes were defined as follows: *right dominant form has been defined as the presence of isolated ARVC 2010 morphological TFC*; a *biventricular form has been defined as the presence of ARVC 2010 morphological TFC and the contextual presence of an LVEF ≤50% or LV LGE*; a *left dominant form has been defined as the presence of a LVEF ≤50% or LV LGE in the absence of any ARVC 2010 morphological TFC*

Table 2

Myocarditis clinical presentation and treatment features by patients and myocarditis-like episodes

DSPMyo+ Cohort Patients (n=177)	
Myocarditis as first presentation, n (%)	107 (60.5)
Myocarditis alone	100 (56.5)
Myocarditis + VT/VF	7 (4.0)
Frequency of myocarditis episodes:	
Patient frequency, n(%)	
Pt with 1 episode	120 (67.8)
Pt with 2 episodes	36 (20.3)
Pt with 3 episodes	9 (5.1)
Pt with 4+ episodes	12 (6.8)
N of episodes, median [IQR]	1 [1–2]
Patient receiving immunosuppression at any time, n (%)	63 (35.6)
Long-term immunosuppression, n (%)	9 (5.0)
CMR available at first myocarditis episode, n (%)	154 (87.0)
Presence of LGE; n (%)	140 (90.9)
Presence of edema, n (%)	127 (82.5)
Lake Louise Criteria met, n (%)	141 (91.6)
EMB available at first myocarditis episode*, n (%)	54 (30.5)
Confirmatory for myocarditis (inflammation), n (%)	46 (85.2)
Fibro-fatty replacement, n (%)	35 (64.8)
Treatment of first myocarditis episode, n(%)	
Immunosuppression	56 (31.6)
NSAIDs/Colchicine	32 (18.1)
None	89 (50.3)
Myocarditis-like Episodes (n=290)	
Chest pain, n (%)	270 (93.1)
Palpitations, n (%)	97 (33.4)
Dyspnea, n (%)	106 (36.6)
Therapy per episode, n(%)	
Immunosuppressive therapy, n (%)	106 (36.6)
Single agent, n (%)	75 (25.9)
Corticosteroid	64 (22.0)
MMF	4 (1.4)
AZT	2 (0.7)
IVIG	3 (0.1)
Anakinra	2 (0.1)
Multiple agents, n (%)	31 (10.7)

DSPMyo+ Cohort Patients (n=177)	
Corticosteroid + AZT	17 (5.9)
Corticosteroid + MMF	7 (2.4)
Corticosteroid + IVIG	3 (0.1)
Corticosteroid + AZT + MMF	2 (0.1)
Corticosteroid + Anakinra + MMF	1 (0.1)
4+ agents	1 (0.1)
NSAIDs, n (%)	47 (16.2)
Alone	29 (10.0)
Colchicine, n (%)	46 (15.9)
With NSAIDs	9 (3.1)
Alone	11 (3.8)

AZT: azathioprine; CMR: cardiac magnetic resonance; IVIG: intravenous immunoglobulin; EMB: endo-myocardial biopsy; LGE: late gadolinium enhancement; MMF: mycophenolate mofetil; NSAIDs: non-steroidal anti-inflammatory drugs; VF: ventricular fibrillation; VT: ventricular tachycardia; details regarding dosages have been reported in TableS6. Long-term was defined as >6 months duration or longer than an initial corticosteroid taper course. *N=34 were retrieved from the RV and N=20 were retrieved from the LV

Table 3

Longterm follow up outcomes of the *DSP*Myo+ cohort, stratified by use of immunosuppressive treatment at the time of a myocarditis-like episode

	Outcomes			p
	DSP Myo+ (n=177)	DSP-Myo+ treated (n=63)	DSP-Myo+ not treated (n=114)	
Follow up time (years), median [IQR]	6.4 [4.0–10.5]	6.5 [3.6–10.6]	6.4 [4.0–10.5]	0.919
VA events, n (%)	69 (39.0)	9 (14.3)	60 (52.6)	<0.001
Rapid arrhythmia, n (%)	34 (19.2)	6 (9.5)	28 (24.6)	0.015
HF Hospitalizations, n (%)	43 (24.3)	6 (9.5)	37 (32.5)	0.001
Myocarditis episodes at follow up, median [IQR]	1 [0–1]	1 [0–1]	1 [0–1]	0.080
LVAD/HT/Death, n (%)	15 (8.44)	3 (4.8)	12 (10.5)	0.187
LVAD, n (%)	1 (0.6)	0	1 (0.9)	1.000
HT, n (%)	13 (7.3)	2 (3.1)	11 (9.6)	0.141
Death, n (%)	2 (1.1)	1 (1.6)	1 (0.9)	1.000

HF: heart failure; HT: heart transplant LVAD: left ventricular assist device; VA: ventricular arrhythmia.