Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Role of Immunosuppression in Patients with Inflammatory Dilated Cardiomyopathy: Meta-Analysis of Randomized Controlled Trials

Rajiv Gupta[1], Harsh Bala Gupta[2], Rahul Chaudhary[3], Roshni N Patel[4], Rahul Gupta[5], Brijesh Patel[6]

[1]Department of Surgery, Adesh Medical College and Hospital, Kurukshetra, India.
[2]Department of Medicine, Government Medical College, Amritsar, India.
[3]Department of Medicine, Mayo Clinic School of Medicine, Rochester, United States.
[4]Muhlenberg College, Allentown, United States.
[5]Department of Medicine, Westchester Medical Center, Valhalla, United States.
[6]Department of Cardiology, West Virginia University, Morgantown, United States.

Received: September 2019
Accepted: September 2019

ABSTRACT

Background: Role of immunosuppression treatment in patients with inflammatory dilated cardiomyopathy is controversial. The aim of this review is to summarize current evidence for immunosuppressive therapy in inflammatory cardiomyopathy. **Methods:** A systematic literature search was performed using PubMed, Embase and MELDINE to identify trials comparing immunosuppressive therapy with either placebo or conventional medical therapy in adult patients with inflammatory cardiomyopathy. Combined primary outcome in our study was all cause mortality and heart transplantation. Secondary outcomes included improvement in left ventricular ejection fraction (LVEF) and left ventricular end diastolic dimension (LVEDD). **Results:** Five randomized controlled trials (RCTs) were identified and four trials with similar comparable groups, with a total of 359 adult patients were included for analysis. Pooled data demonstrated no reduction in all-cause mortality and heart transplantation amongst the immunosuppression or the placebo arm (OR 0.98, 95% CI 0.48-1.98). There was a significant improvement in LVEF (1.34%, 95% CI 0.37-2.30) in patients treated with immunosuppressive medications, however no difference was observed in LVEDD [-0.11mm (95% CI -1.92 – 1.71)] in the treatment arm. **Conclusion:** There was no survival benefit or reduction in heart transplantation events with a significant improvement in LVEF in inflammatory cardiomyopathy patients treated with immunosuppression therapy.

Keywords: Inflammatory cardiomyopathy, immunosuppression, heart transplant, left ventricular ejection fraction.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a heterogeneous group of disorders with an incidence of 148 cases per 100,000 individuals in USA and approximate prevalence of 920 cases per 100,000. It is the third most common cause of heart failure.[1,2] There are many etiologies of dilated cardiomyopathy including, and not limited to, myocarditis, ischemic heart disease, toxin-mediated, familial, peripartum cardiomyopathy, HIV infection, idiopathic or immune mediated. About 20 to 30% of these cases are thought to be secondary to myocarditis. The cause of myocarditis remains unknown with numerous factors shown to be associated with myocardial inflammation, like infection, toxins or injuries. The course of this disease is unpredictable, ranging from relatively mild to rapid severe progressive heart failure and death. Typically, prognosis is poor with 5-year mortality rate of 46%.[2]

Pre-clinical studies report a strong association between infectious agents and immune mediated myocardial damage.[3,4] Also, activation of cellular and humoral autoimmunity has been strongly implicated in chronic inflammatory myocardial disease regardless of the underlying cause.[5,6] Multiple single and multi-centered trials exploring treatment strategies with nonselective anti-inflammatory agents continue to show controversial and inconclusive results.[7] To date, the leading hypothesis for pathophysiology of inflammatory cardiomyopathy is autoimmune activation. This supports the theoretical advantage of using immunosuppressive agents in patients with inflammatory dilated cardiomyopathy. However, multiple randomized controlled trials conducted in last 2 decades have failed to demonstrate immunosuppressive therapy efficacious. The aim of

Name & Address of Corresponding Author
Dr. Harsh Bala Gupta
Associate Professor, Department of Medicine
Government Medical College
Amritsar, Punjab, India 143001.

this study is to analyze the current evidence for role of immunosuppressive therapy in management of inflammatory cardiomyopathy through a meta-analysis of randomized controlled trials in patients with inflammatory dilated cardiomyopathy. We recognize that the last meta-analysis on this subject was done in 2005 by Liu et al; however since new data has been added to the literature, we believe this meta-analysis contains the most updated information.[8]

MATERIALS AND METHODS

Search Strategy

A search of PubMed, EMBASE, the Cochrane Controlled Trial registry, US Clinical Trials databases was performed until May 2, 2018 using these key terms: myocarditis, cardiomyopathy, and immunosuppressive agents, along with individual drug or class names (azathioprine, cyclosporine, immunoglobulin, gamma globulin, interferon, corticosteroid, or prednisone). No language limitations were imposed in the search strategy. Reference lists of included articles were also examined for additional studies. To identify studies reported only in scientific meetings, we performed electronic search of the annual scientific sessions of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology. The search strategy, study selection and analysis were carried out in accordance with the PRISMA statement for systematic reviews [Figure 1].

Study Selection

All selected abstracts and titles were independently scanned by two reviewers (RG and RC) to identify papers for potential inclusion. Studies included in this analysis were required to have: a) randomized controlled study design; b) a clearly defined comparison group (immunosuppressive agents versus conventional heart failure (HF) therapy) c) outcome data available such as mortality, cardiac transplantation, left ventricular ejection fraction (LVEF), and left ventricular end diastolic dimension (LVEDD). This review incorporates only those randomized controlled trials for analysis, which reported baseline and follow up data for both immunosuppressive and control groups. Observational studies and case reports were not included for the analysis. Patients with dropouts or withdrawals were excluded from our study. Studies in which diagnosis of inflammatory cardiomyopathy was established by histological, immunological, and immunohistochemical criteria were included in our analysis. All trials in which inflammatory cardiomyopathy was due to bacteria, protozoa or drug toxicity were excluded from our analysis.

Data extraction and risk of bias assessment

Clinical and outcome data were extracted from individual studies by 2 independent abstractors (RG and RC) and entered into a data extraction form. This included information about study design, patient characteristics (age, immunosuppressive strategy, mortality, cardiac transplant, LVEF, and LVEDD). Jadad score was calculated to assess the quality of included studies.

Statistical Analysis

Statistical Analysis was performed using STATA version 13.0 [StataCorp. 2009. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP] and using Cochrane Collaborative software, RevMan 5.3. All p-values were two-tailed with statistical significance < 0.05 and confidence intervals (CI) computed at 95% level. Measure of heterogeneity between the studies was assessed using the chi square test and was considered significant if p values < 0.10 or $I2 > 25\%$.

Outcome Variables

Primary outcome of interest was all cause mortality and cardiac transplant. Other clinical outcomes studied were change in LVEF, and change in LVEDD. Odds Ratio (OR) and their respective 95% confidence intervals (CI) were estimated for each study and for the analysis of primary and individual clinical outcomes. Random effects model described by Der-Simonian and Laird was used for our main analysis.

RESULTS

Five prospective randomized controlled trials with a total of 359 adult patients were included in the analysis. Out of the five studies, one was double-blinded to groups and outcomes, one was blinded for outcomes and three were not blinded.[9-13] The baseline demographics of the study population in the included trials and their calculated Jadad score are described in [Table 1].

Immunosuppressive therapy used in trials:

Two trials used prednisone alone (10, 13); 2 trials used prednisone in combination with azathioprine (9, 11) and 1 trial compared prednisone in addition to azathioprine and cyclosporine in different arms (12). None showed any benefit in reducing mortality or cardiac transplant.

Death and heart transplantation (4 trials)

Out of the five trials, only four trials reported data on mortality and heart transplant specific to inflammatory cardiomyopathy. There were a total of 48 deaths and heart transplants in the immunosuppression arm (48 of 151) as compared to 39 of 135 in non-immunosuppression arm. Overall there was no statistical significant reduction in mortality or heart transplant between the immunosuppressive and non-immunosuppressive arm (OR 1.00, 95% CI 0.46 – 2.16). There was no evidence of heterogeneity ($I2= 37\%$, $p=0.19$) [Figure 1].

Table 1: Baseline demographics of included studies and Jadad score

Name of trial (study/control)	Age (95%CI or SD)		Sex F/M		LVEF (%)		NYHA III/IV (%)		Jadad score
	Study	Control	Study	Control	Study	Control	Study	Control	
Wojnicz et al (41/43)	41 (16, 61)	39 (29, 60)	9/32	6/37	23.8 ± 8.6	24.9 ± 7.3	80	72	1
Latham et al (7/5)	41 (20, 68) OP		NA	NA	21 ± 9 OP		79% OP		3
Frustaci et al (43/42)	44 ± 16	41 ± 15	18/25	16/26	26.5 ± 6.6	27.7 ± 6.4	49	38	5
Mason et al (54/35)	43 ± 14	41 ± 13	NA	NA	24 ± 11	24 ± 9	47	56	3
Parrillo et al (49/52)	43 (23, 67) OP		NA	NA	17 (3, 35) OP		NA	NA	3

CI =Confidence Interval; SD=Standard Deviation; F=Female; M=Male; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association; NA= Not Available; OP= Overall population

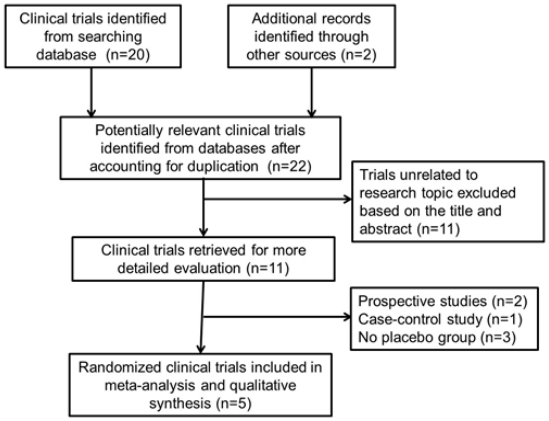

Figure 1: Process of study selection for randomized and prospective trials (PRISMA Statement)

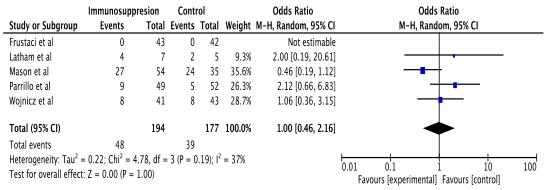

Figure 2: Forest plots demonstrating primary outcome of interest (composite of all-cause mortality and cardiac transplant) in patients with inflammatory dilated cardiomyopathy

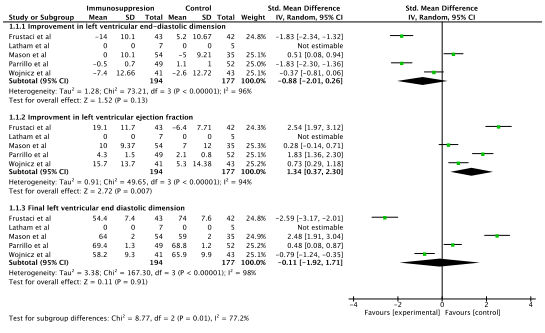

Figure 3: Forest plots demonstrating change in LVEF and change in LVEDD in patients with inflammatory dilated cardiomyopathy

Left Ventricular Ejection Fraction (4 trials)

Left ventricular ejection fraction was assessed in four out of five trials. Immunosuppressive treatment was seen to improve LVEF (evaluated over a period of 6 months) by 1.34 % as compared to non-immunosuppression arm (95% CI 0.37-2.30). However, among the four studies an evidence of heterogeneity was observed which could not be explained by baseline clinical characteristics (I^2 = 94%, p<0.001) [Figure 2].

Left Ventricular End Diastolic Diameter (4 trials)

All but one trial by Mason et al demonstrated a significant improvement in LVEDD in short term. Our study demonstrated that there was no significant improvement in LVEDD with short-term immunosuppression (-0.88 mm, 95% CI -2.01 - 0.26). Statistically significant heterogeneity was detected in our analysis (I^2 = 96%, p<0.001). Interestingly, there was no statistical significant improvement in final LVEDD (-0.11 mm, 95% CI -1.92 – 1.71) with statistical significant heterogeneity (I^2 = 98%, p<0.001).

DISCUSSION

To date, this is the largest meta-analysis analyzing the treatment effect of immunosuppressive therapies in patients with inflammatory cardiomyopathy. The findings of our study demonstrates 1) no significant mortality benefit in patients with inflammatory cardiomyopathy receiving immunosuppressive therapy when compared to conventional medical therapy; 2) an improvement in LVEF with immunosuppressive therapy but with a significant test of heterogeneity; and 3) no improvement in the LVEDD and final LVEDD in the immunosuppressive arm. Our study included five randomized clinical trials; their findings and immunosuppressive regimens used are summarized below.

The earliest trial included in our study is from April 1989 by Latham et al. Latham et al evaluated 52 patients with a recent diagnosis of idiopathic dilated cardiomyopathy. Patients were randomly assigned to conventional HF therapy versus conventional medical therapy along with 50 mg prednisone/day for 2 weeks followed by 40 mg/day for 2 weeks, followed by 30 mg/day for 4 weeks and finally 20 mg/day for 2 more weeks. Prednisone was eventually tapered off over the final 2 weeks.

Overall, addition of prednisone to conventional medical therapy was not associated with improved survival at the end of 2 years. Two patients in the control arm (died=1, transplant=1) and 4 in the treatment arm (died=3, transplant=1) achieved clinical end point.[10]

In Oct 1989 another trial by Parrillo et al studied 102 patients with idiopathic dilated cardiomyopathy to receive prednisone plus conventional heart failure regimen or conventional medical therapy alone. All the patients were further subdivided into 2 prespecified subgroups: reactive or non-reactive based on the results of endomyocardial biopsy. Fifty-two patients (including both reactive and non-reactive) received conventional therapy and remaining (n=49) were treated with prednisone in addition to conventional therapy. The mean ejection fraction demonstrated a trend towards improvement in the prednisone arm as compared to control group (4.3% increase in the ejection fraction as compared to 2.1% increase in the control arm, p=0.054). There was also a trend towards improvement in LVEDD in the treatment arm versus control arm (69.8 mm to 69.4 vs. 67.7 to 68.8, p=0.088 respectively).[13]

Following this trial Mason et al explored different regimens of immunosuppressive therapy in another trial of 111 patients. Patients were randomized to conventional medical therapy or conventional medical therapy plus 24-week immunosuppression regimen. Immunosuppressive regimen consisted of two different protocols. One group received 1 mg/kg of azathioprine twice daily for 24 weeks along with prednisone at 1.25 mg/kg/day in divided doses and maintained at that level for a week. The dose was subsequently reduced by 0.08 mg/kg/week until the dose was 0.33 mg/kg/day at the end of week 12. This dose was maintained until week 20, following which it was reduced by 0.08 mg/kg/week until the end of week 24, following which drug was discontinued. The other protocol consisted of cyclosporine at 5 mg/kg twice daily (to maintain blood cyclosporine level of 200-300 ng/ml at the end of week 1). The dose was reduced to maintain a blood level between 100-200 ng/ml from week 2 - week 4. Subsequently, until end of week 24, dose was further tapered to maintain levels between 60 - 150 ng/ml. The dosing strategy of prednisone was similar to azathioprine initially, however after 1 week the dose was tapered to 0.15 mg/kg/day by end of the week 3. This dose was maintained until week 23 and halved for a week and discontinued by end of week 24. Left ventricular end diastolic dimensions were higher in the immunosuppression arm as compared to control arm (64 mm versus 59 mm, p=0.05). The mean change in LVEF at the end of week 28 was not significantly different in both the groups. The study also did not demonstrate a survival benefit between two groups (p=0.96). Twenty seven patients either died or had cardiac transplant in the immunosuppression group as compared to 24 patients in the control group at the end of 2 years follow up.[12]

In 2001, Wojnicz et al identified 202 patients with inflammatory cardiomyopathy, of which 84 patients with increased HLA expression were randomized to either receive conventional medical therapy (n=43) (beta-blockers, angiotensin converting enzyme inhibitors, digitalis, spironolactone, nitrates and anti-arrhythmic agents) or immunosuppressive therapy (n=41) (prednisone and azathioprine added to conventional therapy). Prednisone was started at a dose of 1mg/kg/day. After 12 days, the dose of prednisone was tapered every 5 days by 5mg/day until reaching the maintenance dose of 0.2mg/kg/day for a total of 90 days. Azathioprine was dosed at 1mg/kg/day for a total of 100 days. Study demonstrated improvement in mean ejection fraction at the end of 6 months and 2 years (39.5 ± 10.7 and 43.9 ± 9.1, respectively) in the immunosuppression arm as compared to control group (30.2 ± 12.4 and 30.9 ± 13.6, respectively). Cardiac death, heart transplantation, or readmission to hospital due to HF was seen in 2 patients in the immunosuppressive arm as compared to 5 cases in placebo arm at the end 6 months. At the end of follow up, 8 patients in each arm achieved the clinical end point.[9]

Frustaci et al, in 2009, enrolled 85 patients prospectively in a randomized placebo controlled trial, of which 43 patients were treated with prednisone (1 mg/kg daily for 4 weeks followed by 0.33 mg/kg daily for 5 months) and azathioprine (2 mg/kg for 6 months) in addition to conventional medical therapy and 42 patients were treated with placebo along with conventional therapy. Study demonstrated a significant improvement in LVEF at the end of 6 months (45.6 % in the treatment arm versus 21.3% in the control arm, $p < 0.001$). There was also a reduction in LVEDD at the end of 6 months (54.4 mm versus 74 mm, treatment versus control arm respectively).[11]

The last meta-analysis on this topic was performed by Liu et al in 2005 with 316 patients comparing conventional medical therapy with immunosuppressive therapy versus placebo. They found no improvement in all-cause death and heart transplantation with use of immunosuppressive therapy (OR= 1.03, 95% CI 0.58 to 1.80). They also assessed effects of immunosuppression on LVEF and LVEDD. LVEF was mildly improved with immunosuppressive therapy (5.06%, 95% CI -0.07% to 10.18%); however, no improvement was noted in LVEDD either in the short-term (-0.87 mm; 95% CI, -8.29 to 6.55) or long-term (-0.52 mm, 95% CI -3.64 to 2.60) with immunosuppressive therapy.[8] The results of this study confirm with our findings and add more convincing data to the literature against any benefit from immunosuppressive regimen in inflammatory cardiomyopathy. Our study only included randomized controlled trials in adult patient

population as opposed to the meta-analysis by Liu et al.

Currently, the only treatment option shown to lengthen survival in patients suffering from inflammatory cardiomyopathy is heart transplantation. Based on the results of our study, the chemotherapy regimens do not appear to increase survival in this patient population. However, these results need to be interpreted carefully as this analysis compared different chemotherapy agents ranging from prednisone, azathioprine and cyclosporine and at different dosing regimens. Also, it can be argued that the selected patient population for the participant studies was at an advanced stage of disease process and an intervention earlier in the time-course of natural history of the disease would have yielded different outcomes.

Although there was no mortality benefit seen, our study did observe an increase in the LVEF. This finding was clouded by presence of significant heterogeneity between trials. In fact, LVEF was seen to improve in both groups- with or without immunosuppressive therapy in the study by Mason et al.[12] A likely explanation for a significant test of heterogeneity is the differences in protocol-assigned definition of "improvement" in left ventricular parameters amongst participant studies and inter-user variability in reading echocardiograms.

Limitations

A major limitation of our study is the power of our study since we were only able to include five trials. Also, significant heterogeneity was observed in the improvement of LVEF. The results of this study need to be carefully interpreted as the participant studies used different immunosuppressive agents at different dosing regimens.

CONCLUSION

In conclusion, immunosuppressive therapy does not confer mortality benefit or reduce need for heart transplantation in patients with inflammatory cardiomyopathy. However, this meta-analysis shows an association with improvement in LVEF, which is sustained at 2 years of follow-up. These results need to be cautiously interpreted because of subtle differences in the methods of the different studies included.

REFERENCES

1. Epidemiology of Dilated Cardiomyopathy. Keane: Nadas' Pediatric Cardiology, 2nd ed.
2. Cardiomyopathy. (2012). Retrieved June 25, 2015, from https://www.clinicalkey.com/topics/cardiology/cardiomyopathy.html
3. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med. 1994;23:1564–1575.
4. Feldman AM, McNamara D. Myocarditis. N Engl J Med. 2000;19: 1388–1398.
5. Feldman AM, McNamara D. Myocarditis. N Engl J Med. 2000;19: 1388–1398.
6. Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death. Learning from the past for the future. Circulation. 1999;99:1091–1100
7. X. Fan, F. Takahashi-Yanaga, S. Morimoto, D.Y. Zhan, K. Igawa, K. Tomooka, et al. Celecoxib and 2,5-dimethyl-celecoxib prevent cardiac remodeling inhibiting Akt-mediated signal transduction in an inherited dilated cardiomyopathy mouse model. J Pharmacol Exp Ther, 338 (2011), pp. 2–11
8. Liu C, Chen J, Liu K. Immunosuppressive treatment for inflammatory cardiomyopathy: meta-analysis of randomized controlled trials. Int Heart J. 2005;46:113–122.
9. Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, et al. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. Circulation.2001;104:39–45.
10. Latham RD, Mulrow JP, Virmani R, et al. Recently diagnosed idiopathic dilated dilated cardiomyopathy: incidence of myocarditis and efficacy of prednisone therapy. Am Heart J. 1989;117:876–882
11. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: The TIMIC study. Eur Heart J 2009; 30: 1995–2002
12. Mason JW, O'Connell JB, Herskowitz A, et al, for the Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:269-75
13. Parrillo JE, Cunnion RE, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. N Engl J Med 1989;321:1061-1068

How to cite this article: Gupta R, Gupta HB, Chaudhary R, Patel RN, Gupta R, Patel B. Role of Immunosuppression in Patients with Inflammatory Dilated Cardiomyopathy: Meta-Analysis of Randomized Controlled Trials. Ann. Int. Med. Den. Res. 2019; 5(6):SG10-SG14.

Source of Support: Nil, **Conflict of Interest:** None declared