Immunosuppressive treatment for inflammatory cardiomyopathy: meta-analysis of randomized controlled trials

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CRD summary
This review concluded that there was no evidence that immunosuppressive therapy improves survival in patients with inflammatory cardiomyopathy. The review had its limitations, but the authors' conclusions about the lack of evidence of effect on mortality were supported by the review and are likely to be robust for adult populations.

Authors' objectives
To assess the efficacy of immunosuppressive treatment in patients with inflammatory cardiomyopathy.

Searching
MEDLINE and CINAHL (both from inception to February 2004) and the Cochrane CENTRAL Register (Issue 1 2004) were searched for studies reported in any language; the search terms were reported. The reference lists of included studies were also checked. Authors of primary studies were contacted for clarification of data.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion, regardless of the use of blinding. The included studies followed up patients from 1 year to more than 2 years.

Specific interventions included in the review
Studies that compared immunosuppressive treatments with placebo or conventional treatment for at least 4 weeks were eligible for inclusion. The studies included in the meta-analysis used prednisone alone or in combination with azathioprine or cyclosporine. The duration of the trials ranged from 10 weeks to 8 months.

Participants included in the review
Studies in patients with inflammatory cardiomyopathy were eligible for inclusion. The studies had to diagnose inflammatory cardiomyopathy using established histological, immunological and immunohistological criteria. Studies that only included patients with inflammatory cardiomyopathy due to bacteria, protozoa or drug toxicity were excluded. Studies including a mix of patients with inflammatory and idiopathic dilated cardiomyopathy were only included if the results for patients with inflammatory cardiomyopathy could be extracted.

Outcomes assessed in the review
Studies that reported deaths and drop-outs were eligible for inclusion. The primary outcome was all-cause death and heart transplantation. The secondary outcomes were left ventricular ejection fraction (LVEF) and left ventricular end diastolic dimension (LVEDD). Adverse effects were also assessed.

How were decisions on the relevance of primary studies made?
The studies were selected by consensus.

Assessment of study quality
The studies were assessed for adequacy of randomisation and concealment, blinding during treatment and outcome assessment, description of withdrawals and drop-outs, and analysis on an intention-to-treat (ITT) basis. Two reviewers assessed validity. Any disagreements were resolved through consensus or by a third reviewer.
**Data extraction**

Two reviewers independently extracted the outcomes data. Any disagreements were resolved through consensus or by a third reviewer. Odds ratios (ORs) for dichotomous data and weighted mean differences (WMDs) for continuous data were calculated, along with their 95% confidence interval (CI), for each study.

**Methods of synthesis**

How were the studies combined?

Pooled ORs and 95% CI were calculated for dichotomous data and pooled WMDs and 95% CI for continuous data. The studies were pooled using random-effects and fixed-effect models. The authors stated that where there were no clinically important differences between the studies, the studies were pooled using a random-effects model. Outcomes for mortality were calculated on an ITT basis, categorising all drop-outs or withdrawals as deaths. There were insufficient data to analyse LVEF and LVEDD on an ITT basis.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the Q test and the I-squared statistic (heterogeneity was considered significant if $P<0.10$ or $I^2>25\%$). Where heterogeneity was found, study quality and clinical characteristics were examined. Pre-planned subgroup analyses were used to examine the influence on the outcomes of age (children younger than 18 years and adults aged 18 or over), duration of follow-up for LVEF and LVEDD (short term defined as 28 weeks or less and long term defined as more than 28 weeks) and method of analysis (ITT and not ITT).

**Results of the review**

Five trials ($n=316$) were included: 4 RCTs (266 adults) and 1 quasi-RCT (50 children).

Of the 5 included studies, one was blinded to treatment and outcome assessment, two reported using an appropriate method of allocation concealment, and one used an ITT analysis for one outcome. All 5 trials reported drop-outs and/or withdrawals.

Death and heart transplantation (4 trials, $n=257$).

There was no significant difference in death and heart transplantation between immunosuppressive and non-immunosuppressive treatment (OR 1.03, 95% CI: 0.58, 1.80). No statistically significant heterogeneity was detected ($P=0.52$, $I^2=0\%$). The results were similar for adults and children.

LVEF (4 trials).

Immunosuppressive treatment increased short-term LVEF by 5.06% (95% CI: -0.07, 10.18), but this increase was not statistically significant. Heterogeneity between the 4 studies ($P=0.14$, $I^2=48.7\%$) could not be explained by baseline clinical characteristics or quality.

There was no significant difference in long-term LVEF between immunosuppressive and non-immunosuppressive treatment in adults (OR 4.45%, 95% CI: -5.25, 14.15). The only study in children was small and quasi-randomised and thus provided limited evidence.

LVEDD (4 trials).

There was no statistically significant difference between treatments in adults in the short term (WMD -0.87 mm, 95% CI: -8.29, 6.55) or in the long term (WMD -0.52 mm, 95% CI: -3.64, 2.60). Statistically significant heterogeneity was detected for both meta-analyses ($P=0.001$, $I^2=84.8\%$ and $P=0.0005$, $I^2=86.9\%$, respectively).

Side-effects (2 trials).

Side-effects were reported in 43% (39 out of 90) of patients treated with immunosuppressives. Prednisone-related weight gain (greater than 5 kg) was common. Less common side-effects were hypertension, hyperglycaemia and infection.
Authors’ conclusions
There was no evidence that immunosuppressive therapy improved survival in patients with inflammatory cardiomyopathy.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria for the participants, intervention, outcomes and study design. Three relevant databases were searched and attempts were made to minimise language and publication bias. Methods were used to minimise errors and bias in the study selection, validity assessment and data extraction processes. Validity was assessed using established criteria. Clinical and statistical heterogeneity were assessed, and where heterogeneity was found potential reasons for it were explored. Some meta-analyses (LVEF and LVEDD) showed significant heterogeneity, with studies showing different directions of treatment effect; it might not have been appropriate to pool these studies. In addition, it seemed that there was no consistency in the use of fixed-effect and random-effects models, as both were used whether heterogeneity was observed or not. The authors’ conclusions about the lack of evidence of effect of immunosuppressives on mortality were supported by the evidence obtained for adults and are likely to be robust. However, owing to the lack of primary studies, it is unclear whether they are also applicable to children.

Implications of the review for practice and research
Practice: The authors stated that heart transplant is currently the only treatment that can lengthen the survival of patients with final stage inflammatory cardiomyopathy. Current treatment therefore appears to be limited to supportive therapies or heart transplantation.

Research: The authors did not state any implications for further research.

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