

Immunosuppressive therapy in acute myocarditis: an 18 year systematic review

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Background: Immunosuppressive therapy is reportedly ineffective in adults with acute myocarditis.

Aims: To systematically review the impact of immunosuppressive therapy on the outcome of acute myocarditis in children.

Methods: A literature search for articles published from 1984 to 2003 was conducted with the following keywords: myocarditis, dilated cardiomyopathy, and immunosuppression. The relevant studies were systematically reviewed and comparison of treatment effect was made by calculating the odds ratio (OR) and confidence interval (CI) using the exact method based on the exact discrete reference distribution.

Results: Of the 1470 articles found, only nine studies were eligible. The odds for improvement with immunosuppression was between 4.33 (95% CI 0.52 to 52.23) and 2.7 (95% CI 0.59 to 14.21). Addition of a second immunosuppressive agent to prednisolone only proved effective in one randomised controlled trial (OR 0.09, 95% CI 0.01 to 0.52). Heterogeneity of these studies precluded pooled odds ratio.

Conclusion: Current data suggest that immunosuppressive therapy does not significantly improve outcomes in children with acute myocarditis and there is insufficient evidence for its routine use. However, statistical power to detect a significant difference in the treatment effect may be limited because of the small number of subjects. This, together with problems of diagnosis, varying treatment practices, and a relative lack of evidence based guidelines would support efforts for a large multicentre, randomised controlled trial to better define the role of immunosuppression in acute myocarditis.

Acute myocarditis is a rare inflammatory cardiac disease in adults and children. Its true incidence is difficult to determine and has been estimated between 0.15% and 0.6%^{1,2} in the overall population. A recent study by Soongswang and colleagues³ showed that myocardial diseases made up 1.2% of all cardiovascular diseases in Thai children, and myocarditis accounted for 27.3% of these myocardial diseases.

Acute myocarditis is defined on histology as inflammation of the myocardium associated with myocellular necrosis. The gold standard for diagnosis of acute myocarditis is an endomyocardial biopsy. The Dallas criterion⁴ has been widely used, but in 1995, the World Health Organisation/International Society and Federation of Cardiology Task Force (ISFC) on the Definition and Classification of Cardiomyopathies came up with the following recommendations. Changes on the first endomyocardial biopsy was defined by: acute (active) myocarditis (clear cut infiltrate of ≥ 14 leucocytes/mm² with necrosis and degeneration), chronic myocarditis (infiltrate of ≥ 14 leucocytes/mm² but usually without necrosis and degeneration), and no myocarditis (no infiltrating cells or < 14 leucocytes/mm²).⁵ Drugs, toxins, and autoimmune and systemic diseases can also cause acute myocarditis, but it is commonly due to infectious agents.⁶ In Europe and the United States, Coxsackie viruses and adenoviruses predominate, but pathogens in the developed countries include *Trypanosoma cruzi* and *Corynebacterium diphtheriae*.

The pathogenesis of viral myocarditis is now recognised to have three distinct phases: viral replication, autoimmune injury to the myocytes, and dilated cardiomyopathy.⁷ The autoimmune phase is believed to play a major role and the use of immunosuppressive agents may be useful in containing myocyte destruction. Following reports on the treatment of viral myocarditis with prednisolone, many studies have been done in a bid to establish the usefulness of immuno-

suppressive therapy in this setting.^{8–13} In the adult population, two large randomised controlled trials (European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease,^{14,15} and the Myocarditis Treatment Trial^{16–18}) and two meta-analyses^{19,20} failed to show any significant benefit with immunosuppression. Thus, supportive treatment (anti-failure and antiarrhythmic therapy) continues to be the cornerstone in the management of acute myocarditis, at least in adults.

Currently, there are no clear evidence based guidelines for the use of immunosuppressive therapy in children with myocarditis. Children are not merely small adults, and the results in the adult population should not be conveniently extrapolated to the paediatric population. Furthermore, the aetiology and pathophysiology of myocarditis, its effects on a growing heart, and the response to treatment in a child may differ significantly from that of the adult. As of 1991, several studies in children have been reported and various treatment regimes tried, with prednisolone being the most widely used immunosuppressant. However, many are small studies that are inadequately powered to provide clear guidance.

Our objective was to systematically review the evidence currently available for the use of immunosuppression in children with acute myocarditis and determine its effect on the outcome of acute myocarditis. The effect of adding a second immunosuppressive agent to prednisolone was also evaluated.

METHODOLOGY

Search strategy

A literature search for articles published in English between January 1984 and December 2002 was conducted via PubMed using the following keywords: myocarditis, immunosuppression, dilated cardiomyopathy. We also searched the Cochrane Trials Register from the Cochrane Library and the references

of several key articles to ensure that eligible studies were not missed. This was limited to studies done on human paediatric subjects aged below 18 years. The preliminary search did not yield any study on the use of immunosuppressive agents in children with acute myocarditis prior to 1984. Many of the reports involving children which were published subsequently had small sample sizes.

Selection criteria

Studies done solely on children less than 18 years of age (neonatal population excluded) were identified and included in the analysis. Studies with cohorts made up of a heterogeneous population of mainly adults and small numbers of paediatric subjects were excluded because it made comparisons difficult.^{21, 22}

The diagnosis of acute myocarditis was made either on endomyocardial biopsy or clinically by the investigators and was considered in patients who presented within two months from onset of symptoms. Clinical findings included the presence of congestive cardiac failure, arrhythmia with no underlying structural abnormality, sudden, unexplained cardiovascular collapse requiring mechanical support such as extracorporeal membrane oxygenation (ECMO) or ventricular assist devices (VAD), or electrocardiograph (ECG) changes consistent with acute myocarditis. Acute (active) myocarditis was defined on the first endomyocardial biopsy by the presence of inflammatory or lymphocytic infiltrates in the myocardium or by the Dallas criteria.

Immunosuppressive or immunomodulatory therapy included the use of prednisolone, azathioprine, cyclosporine A, intravenous immunoglobulin G (IVIG), interferon-alpha, and OKT3.

Eligible studies had at least one of two outcome measures: cardiovascular improvement and survival. The following parameters were used as markers of improvement in cardiovascular status: (1) resolution of symptoms of congestive cardiac failure or arrhythmia; (2) resolution of arrhythmias on ECG; (3) haemodynamic measurements using cardiac catheterisation, two dimensional echocardiography, or radionuclide scans and; (4) resolution of histological findings on repeat endomyocardial biopsy (defined by a decrease in, or an absence of, inflammatory infiltrate in the myocardium or by the Dallas criteria as "healed" or "resolved"). Patients were considered to have survived if they were alive and had avoided heart transplant at the end of the study period as defined by each individual study. Those who died or required heart transplant were considered non-survivors.

This systematic review aimed to focus on randomised controlled trials and case-control studies, but due to the scarcity of existing published data, non-controlled trials, retrospective studies, and larger case series were considered. Isolated case reports and case series with fewer than four subjects were excluded as sufficient size is required in each treatment arm for the statistical power to detect a statistically significant difference. Furthermore, estimate of the treatment effect based on an unduly small sample size is likely to be imprecise. These studies were carefully reviewed and the data analysed with the help of a statistician.

Data collection and analysis

Of the 1470 articles reviewed, only nine studies met the above criteria. We found one randomised controlled trial,²³ one case-control trial,²⁴ one prospective non-controlled trial,²⁵ four retrospective studies,^{26–29} and two case series.^{30, 31} The individual subjects of each study were analysed by a group of three reviewers and a consensus was reached. A comparison was made between treatments, for example, those who received immunosuppressive treatment and those who did

not, and the treatment effect was estimated by calculating the odds ratio (OR) and the 95% confidence interval (CI). As the sample size in most of the studies was small, we used the exact method which was based on the exact discrete reference distribution for calculating the CI.³² This was carried out using the STATXACT software.

RESULTS

All the eligible studies had relatively small sample sizes. The results of each study were reviewed individually. The subjects were further analysed according to treatment groups and their response to various treatment regimes. The total number of eligible subjects from individual studies from January 1984 to December 2002 was 170. The mean follow up period in the studies ranged from 8 to 59.4 months. Tables 1–3 summarise the results of the individual studies.

Improvement after treatment with immunosuppressive therapy in all studies ranged between 68% and 100%; survival with immunosuppressive therapy was 75–100%. A comparison was made between the group receiving treatment with immunosuppressives and that without, with the OR ranging from 0 to 4.33 (table 2). Increased odds of improvement with immunosuppressive agents was observed in the case-control trial and the randomised controlled trial with OR and 95% CI at 2.7 (0.59 to 14.21) and 4.33 (0.52 to 52.23) respectively. However, the improvement was not statistically significant. The OR of some studies could not be estimated as they lacked a control arm and the heterogeneity of the study designs precluded a formal meta-analysis.

As there were various treatment regimes being used, an attempt was made to compare the outcome of the different treatment regimes. Prednisolone was the main immunosuppressive agent used in most studies. A second immunosuppressant (for example, azathioprine^{23, 26, 28, 29} and cyclosporine A^{23, 25}) was added to prednisolone in some studies. The effect of IVIG was studied in isolation²⁴ and OKT3 with treatment regimes akin to heart transplant protocols³¹ was also evaluated.

In the individual studies, the addition of another immunosuppressive agent appeared to be associated with a better outcome. The prospective randomised controlled trial²³ with one control arm and three treatment arms showed that prednisolone alone had similar results to the control. However, when azathioprine or cyclosporine A was added, the outcome improved significantly. The results from the prospective non-controlled trial²⁵ concurred, showing an improvement and survival in all nine patients treated with prednisolone and cyclosporine A. In a case series using OKT3 in conjunction with other immunosuppressive agents, four of five patients had complete recovery of myocardial function,³¹ with three being weaned off temporary mechanical assist devices. One patient had succumbed in the immediate period from a thromboembolus.

We compared the use of prednisolone alone with a combination of prednisolone with other immunosuppressive agents (table 3). Again, due to the heterogeneity of the study designs and treatment protocols, and the lack of a control arm in at least half the studies, it was not appropriate to obtain a pooled OR for all the studies under consideration. Only one study showed a significant benefit with the addition of another agent with an OR of 0.09 (95% CI 0.01 to 0.52).

Very few adverse effects were reported from the use of immunosuppressive treatment, although there may be theoretical concerns about its use in the active phase of infection.

Table 1 Summary of results of individual studies

| Reference | Study design | Controls* | n† | IMST‡ | Improvement with IMST | Survival with IMST | IMSA used |
|-----------------|--------------|-----------|-----|-------|-----------------------|--------------------|-----------|
| Chan, 1991 | RS | No | 13 | 13 | 92% | 92% | P, CyA |
| Drucker, 1993 | CCT | Yes | 46 | 24 | 38% | 80% | IVIG, P |
| Ciszewski, 1994 | RS | No | 19 | 4 | 75% | 100% | P |
| Balaji, 1994 | RS | No | 10 | 8 | 75% | 100% | P, A |
| Camargo, 1995 | PRCT | Yes | 68§ | 38 | 68% | 89% | P, A, CyA |
| Ino, 1995 | CS | No | 10 | 4 | 100% | 100% | P |
| Kleinert, 1997 | PNCT | No | 29 | 9 | 100% | 100% | P, CyA |
| Lee, 1999 | RS | No | 36 | 34 | 74% | 75% | P, A, O |
| Ahdoot, 2000 | CS | No | 5 | 5 | 100% | 80%¶ | O, P |

CS, case series; CCT, case-control trial (using historical controls); PNCT, prospective non-controlled trial; PRCT, randomised controlled trial; RS, retrospective study; IMST, immunosuppressive therapy; IMSA, immunosuppressive agents; P, prednisolone; CyA, cyclosporine A; IVIG, intravenous immunoglobulin G; A, azathioprine; O, others e.g. OKT3, interferon-alpha.

*Original study design included controls.

†Number of patients enrolled in original study.

‡Number of patients receiving immunosuppressive therapy in the study.

§68 children with clinical features of dilated cardiomyopathy, of which 38 with acute myocarditis received immunosuppressive therapy.

¶The single mortality from this study was due to an unrelated cause.

DISCUSSION

There is no evidence for the use of immunosuppressive therapy in children with acute myocarditis from the current available data, and a meta-analysis is not feasible at this point in time due to marked heterogeneity of the available studies in terms of diagnosis, methodology, treatment protocols, and outcome measures. These limitations are elaborated below.

Acute myocarditis rarely occurs in the general population and its true incidence is elusive. Data are often gathered from postmortem examination findings or sudden infant death syndrome and extrapolated to the general population. Individual large scale studies are difficult to conduct, hence the small sample size of the studies reviewed. This has resulted in a lack of statistical power to detect a significant difference in the treatment effect for individual studies and the estimates of the treatment effect based on small sample sizes were imprecise, with wide confidence intervals.

The criteria for enrolment of patients into trials need to be clearly defined. Acute myocarditis is a disease that is difficult to diagnose at initial presentation. Its clinical manifestations are protean and range from subclinical electrocardiograph changes³³⁻³⁵ to acute cardiovascular collapse requiring mechanical support.³⁶⁻³⁸ There may also be over-diagnosis of this condition based purely on clinical grounds.³⁹ Also, its clinical and histological features often overlap with that of dilated cardiomyopathy.

Even when an endomyocardial biopsy specimen is obtained, the diagnosis may still be difficult. Firstly, the myocardial inflammation may not be uniform globally throughout the myocardium, leading to false negatives.

Secondly, disagreements exist among pathologists in the histological interpretation up to 36% of the time, the conflict arising mainly with cases of dilated cardiomyopathy,⁴⁰ and neither the Dallas nor WHO criteria are consistently used worldwide. Thirdly, although polymerase chain reaction (PCR) can be used to detect the common viruses such as Coxsackie, adenovirus, influenza, Epstein-Barr virus, and cytomegalovirus, and giant cell myocarditis can be readily diagnosed on histology, other causes cannot be easily determined. As such, the patient selection criteria in eligible studies in our systematic review were inconsistent. While most studies diagnosed acute myocarditis on endomyocardial biopsy,²³⁻²⁵⁻³⁰ others were based on clinical grounds.²⁴⁻³¹

Apart from two prospective studies²⁴⁻³¹ which directly enrolled patients who presented with acute myocarditis, the other trials selected their subjects from a cohort of patients with pre-existing dilated cardiomyopathy²³⁻²⁵⁻²⁷ or rhythm abnormalities²⁸⁻³⁰ who later proved to have acute myocarditis. The latter methodology subjects a study to sampling bias.

The response to immunosuppression can vary according to the underlying aetiology. A patient with myocarditis from *Trypanosoma cruzi* or *Corynebacterium diphtheriae* may respond differently to one with enterovirus myocarditis. Also, patients with an underlying inflammatory disorder or giant cell myocarditis may benefit more from immunosuppression.⁴¹ A conscious effort was attempted to analyse the subgroups, but all the eligible studies failed to specify the underlying aetiology of acute myocarditis.

Table 2 Improvement with and without immunosuppressive treatment (IMST)

| Reference | Improvement with IMST | Improvement without IMST | OR (95% CI) |
|------------|-----------------------|--------------------------|----------------------|
| Chan* | 12/13 | 0/0 | – |
| Drucker | 9/24 | 4/22 | 2.7 (0.59 to 14.21) |
| Ciszewski* | 3/4 | 0/0 | – |
| Balaji | 6/8 | 0/2 | – |
| Camargo | 26/38 | 2/6 | 4.33 (0.52 to 52.23) |
| Ino* | 4/4 | 0/0 | – |
| Kleinert* | 9/9 | 0/0 | – |
| Lee | 25/34 | 1/1 | 0 (0 to 112.7) |
| Ahdoot* | 5/5 | 0/0 | – |

*OR and its associated 95% CI cannot be estimated for these studies because there was no control arm. In Balaji *et al*, the OR if estimated was infinity, and cannot be meaningfully interpreted.

Table 3 Treatment with prednisolone alone versus other immunosuppressive agents (IMSA)

| Reference | Improvement with prednisolone alone | Improvement with other IMSA (± prednisolone) | OR (95% CI) |
|------------|-------------------------------------|--|---------------------|
| Chan | 11/12 | 1/1 | 0 (0 to 468.0) |
| Drucker | 0/1 | 9/23 | 0 (0 to 65) |
| Ciszewski* | 3/4 | 0/0 | – |
| Balaji | 4/6 | 2/2 | 0 (0 to 18.92) |
| Camargo | 3/12 | 23/29 | 0.09 (0.01 to 0.52) |
| Ino* | 4/4 | 0/0 | – |
| Kleinert* | 0/0 | 9/9 | – |
| Lee | X/16 | X/18 | – |
| Ahdoot* | 0/0 | 5/5 | – |

*OR and its associated 95% CI cannot be estimated for these studies because there was no control arm. In Lee *et al*, a breakdown of figures (X) for patients who improved on prednisolone alone and others ± prednisolone cannot be obtained.

There is some suggestion that a histological subset of patients respond better with immunosuppressive treatment.⁴²⁻⁴³ In the study by Kleinert and colleagues,²⁵ patients with active myocarditis on histology showed good haemodynamic and clinical response to immunosuppressive treatment, whereas subjects with a similar clinical picture but "borderline" or non-specific findings on histology showed no improvement in LVEDd and FS at their last follow up. The results from Balaji and colleagues²⁸ concurred. Hence, endomyocardial biopsy may prove to be a useful adjunct in guiding the treatment of acute myocarditis despite its inherent risks and complications.⁴⁴

Although all the studies reported good outcomes with immunosuppressive therapy, the results have to be interpreted cautiously. A meta-analysis in adults¹⁹ showed that 58% of acute myocarditis recovered spontaneously, yet most of the paediatric studies lacked control groups. Without comparison between treatment and non-treatment arms, it is difficult to determine the true effectiveness of immunosuppressive treatment as the OR estimate could not be obtained for those studies without controls.

The choice of treatment regime appears to determine the eventual outcome²³⁻²⁵ with different treatment regimes resulting in different outcomes. If the results of the various regimes were pooled together, it would give an idea of the overall effectiveness of immunosuppressive treatment in acute myocarditis. However, a statistically significant treatment effect of one regime may be diluted by results from a less effective treatment regime. The time of initiation of immunosuppressive therapy was often not explicitly stated in most studies.

The survival and clinical status of the patient after an episode of acute myocarditis is of primary importance and this is best correlated with the haemodynamic status, easily assessed by echocardiography (LVEDd, EF, and FS). Resolution from arrhythmia or second cardiac catheterisation was occasionally done, with or without a repeat endomyocardial biopsy. However, improvement in the second endomyocardial biopsy does not always correlate with the clinical status.

Performing a meta-analysis on studies with heterogeneity in patient enrolment, methodology, treatment regime and outcome measure is not feasible with present information. The results have not shown that immunosuppressive therapy improves the outcome of children with acute myocarditis. As with the adult population, anti-failure therapy will continue to be the cornerstone of treatment. However, there are new insights that an autoimmune mechanism is largely responsible in the pathogenesis of acute myocarditis and there may at least be a theoretical role for immunosuppression in certain subsets of patients.

Perhaps the successful use of immunosuppressive therapy in acute myocarditis lies in its appropriate timing. Administration of immunosuppressive agents during the viral replication phase may suppress innate host immune response to eliminate the virus and this would have detrimental effects. However, when the viral killing phase is complete but cardiac auto-antibodies (through molecular mimicry) still persist, immunosuppression would theoretically be beneficial to contain myocyte destruction and hopefully curb its progression to dilated cardiomyopathy.

Conclusion

The routine use of immunosuppressive therapy in acute myocarditis in children cannot be recommended based on the current evidence available and more work in this area needs to be done. As the exact mechanism for myocardial damage unravels, immunosuppressive therapy targeted at specific pathways in the autoimmune cascade during a certain phase

of the clinical illness, rather than in a haphazard manner may be the key in treating this condition. We feel that a multicentre (because of the small numbers involved) randomised controlled trial needs to be conducted to determine the effectiveness of immunosuppressive treatment in children with acute myocarditis.

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ARCHIVIST.....

Cerebral palsy, birthweight, and gestation

Both perinatal death and cerebral palsy are more likely in babies whose birthweight is lower than expected for gestational age but data for lower gestational ages are inadequate. Babies whose birthweight is high for gestational age have an increased risk of perinatal death and possibly of cerebral palsy. Babies who grow slowly in utero are more likely to be born early and therefore weight standards based on birthweight may be too low at earlier gestational ages. In a European collaborative study (Stephen Jarvis and colleagues. *Lancet* 2003;**362**:1106–11, see also commentary, *ibid*: 1089–90) an attempt has been made to circumvent this difficulty by using fetal growth standards based on ultrasound estimations of weight during pregnancy of healthy babies born at term. Data were gathered from 13 cerebral palsy registers in eight countries of which those from three registers in two countries were excluded from the published analysis. The birthweights and gestational ages of 4503 singleton children with cerebral palsy born between 1976 and 1990 were compared with published reference standards from the North of England and from Sweden. Rates of cerebral palsy were calculated from local population data.

Using weight for gestation standards based on birthweight different patterns were seen for babies born before or after 32 weeks gestation. After 32 weeks rates of cerebral palsy were lowest at a weight for gestation Z score of between 1 and 2 (equivalent to 75th to 90th percentile). There was a reverse-J curve with the highest rates of cerebral palsy at very low and very high Z scores. Before 32 weeks the lowest cerebral palsy rates were at weight for gestation Z scores of between –1 and –2 (about 3rd to 10th percentile). Using fetal growth rate standards this different pattern at earlier gestational ages was no longer seen. (This finding seems difficult to explain and they offer no explanation). Now, at all gestational ages there was the same reverse-J curve with the lowest risk of cerebral palsy at Z scores of between 1 and 2. The findings were similar for all types of cerebral palsy. For babies born between 32 and 42 weeks of gestation the risk of cerebral palsy was increased 4–6 fold at birthweights below the tenth percentile compared with birthweights between 25th and 75th percentile. For birthweights above the 97th percentile the increase was 1.6–3.1-fold.

The optimum birthweight for avoiding cerebral palsy is at 75th to 90th percentile for gestational age (using fetal growth standards at lower gestations). The risk is increased at lighter or heavier birthweights for gestational age. Whether abnormal fetal growth is a cause or a result of cerebral palsy is not known and there is uncertainty about whether the abnormal growth is proportionate (affecting all aspects of growth) or disproportionate (affecting mainly weight). Either way, the abnormal growth starts long before birth.