EDITORIAL

Immune suppressive treatment in paediatric myocarditis: still awaiting the evidence

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Is immune suppressive treatment for myocarditis in the paediatric patient helpful?

Paediatric and adult cardiological practices are dominated by (respectively) congenital and atheromatous heart disease. Some diseases are common to both specialities, an example being myocarditis. It is a paradox that a 15 year old child may be given potent immune suppressive treatment for myocarditis but a 16 year old on the adult cardiology ward with the same diagnosis will not. What is the evidence for this conundrum?

FEW PAEDIATRIC STUDIES

In adults a randomised study,[1] ongoing work,[2] review, and meta-analysis[3 4] have shown that immune suppression is not helpful. The paediatric literature is scant. There are five paediatric case series with less than 10 treated cases of myocarditis in each.[5–9] There are two case series from Toronto,[10 11] the more recent including 34 treated cases without controls. The largest paediatric study with controls[12] had some degree of randomisation, but has been criticised in meta-analysis for methodological flaws.[3] Furthermore, this study was set in an area where Chagas disease was endemic and the results are unlikely to apply to European and North American populations where entero-, adeno- and parvovirus infections predominate as causes of paediatric myocarditis.

The paediatric case series have varied clinical and/or histological entry criteria and immune suppressant agents have been used singly or in combination. The data are far too heterogeneous to allow recommendations to be made, although some would argue that dual agent immune suppression appears to be beneficial. A large randomised study is clearly required in the paediatric population.

In this issue Gagliardi and colleagues from Rome reveal their experience with immune suppression for paediatric myocarditis in 114 patients.[13] Frustratingly, the study was not randomised. This causes difficulty in that myocarditis has a spontaneous recovery of 60% in adults.[3] Our centre has reported improving results with aggressive management of end stage dilated cardiomyopathy in children,[14] including bridging children to transplant or recovery with mechanical support. As the young clearly recover from serious illness much more quickly than the old, it would not be surprising if the outcome for myocarditis in previously fit children in the current era was better than the adult value of 60%, even without immune suppression and perhaps close to the 79% reported with immune suppression.[11]

PROGNOSIS FOR DILATED CARDIOMYOPATHY

It has been shown that in children under 2 years of age the prognosis for ''dilated cardiomyopathy'' is better than in older children.[15 16] A possible explanation could be that there is a higher proportion of undiagnosed viral myocarditis (and therefore spontaneous recovery) in an age group (under 2) where viral infections are frequent. The paper from Gagliardi and colleagues[13] would appear to support this as there was a higher proportion of biopsy proven myocarditis in children with a mean age of less than 2 and this group also had a significantly higher rate of recovery of cardiac function.

RISKS OF IMMUNE SUPPRESSION IN MYOCARDITIS

There is a theoretical problem with immune suppression for viral myocarditis. Adults with a more severe histological immune reaction may have a better outcome[1] and immune suppression could in theory impair eradication of viruses from the heart, which could be an explanation for an increased mortality.[17] The paper from Gagliardi and colleagues[13] uses a higher dosage of steroids than that used by many paediatric units (including our own) post-heart transplantation, yet this seems to be well tolerated. It would be premature to claim that this level of immune suppression is a benign treatment and it would be surprising if there are no future complications; however, it is encouraging that it was so well tolerated in over 100 children.

The crossover with transplantation therapy is interesting in that cardiac viral persistence can be a serious problem in the immune suppressed heart.[18] In adults with myocarditis and viral persistence, there has been enthusiasm for treatment with interferon to eradicate the virus.[19] Gagliardi and colleagues[13] did not have the results of polymerase chain reaction (PCR) for common viruses in this paper, nor are the results available of immunoglobulin assays from peripheral blood, so it is conceivable, but unlikely, that all the cases described were non-viral autoimmune cardiomyopathy. A well known example of the latter is giant cell myocarditis, which can respond to immune suppression,[20] yet there were no cases of this reported in the series. It does seem unlikely that patients with a viral persistence will do well with immune

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suppression. In adults there has been encouraging work showing that immune suppression is best suited to patients who do not have virus on PCR and who have anti-cardiac antibodies,[21] and are in the autoimmune stage of myocarditis.[22] There has been concern about creating a chronic myocarditis by using immune suppression. The earlier work from Gagliardi reported this finding at follow up in 10 (50%) of treated children[23]; this is not found in the current paper where only 7 (27%) had persistent myocarditis, which is confusing as it encompasses the earlier era.

PREDICTORS OF SURVIVAL

Echocardiographic predictors of survival in paediatric dilated cardiomyopathy have been reported in detail and those with the worse systolic function tend to have the worse prognosis. The data from Gagliardi and colleagues[13] in this issue concurs with this in that those patients with the lowest ejection fraction had a significantly worse outcome. Of note, this study had an aggressive approach to biopsy, which is often shied away from in paediatric heart failure because of the theoretical risks associated; however, this large series showed that biopsy was safe in the hands of skilled operatives. Interestingly, warfarin was used for anticoagulation regardless of age. Many paediatric cardiologists prefer to use aspirin in young infants because of the difficulties with warfarin; however, it was safe in this series.

CONCLUSION

The current study by Gagliardi and colleagues[13] helps paediatric cardiologists in a number of ways: it confirms that older age and lower ejection fraction at presentation are associated with a worse prognosis, which are useful facts in counselling. The paper may also influence medical management as it has shown that cardiac biopsy and anticoagulation with warfarin are low risk in all age groups. The authors have also shown that double agent immune suppression is safe in the paediatric population. It has failed to show that the prognosis of paediatric myocarditis without immune suppression is worse. The answer to the latter question can only be answered by a large randomised study.

REFERENCES

1 **Mason JW**, O'Connell JB, Herskowitz A, *et al*. A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. *N Engl J Med* 1995;**333**:269–75.
2 **Maisch B**, Hufnagel G, Schonian U, *et al*. The European study of epidemiology and treatment of cardiac inflammatory disease (ESETCID). *Eur Heart J* 1995;**16**(suppl O):173–5.
3 **Maisch B**, Herzum M, Hufnagel G, *et al*. Immunosuppressive treatment for myocarditis and dilated cardiomyopathy. *Eur Heart J* 1995;**16**(suppl O):153–61.
4 **Garg A**, Shiau J, Guyatt G. The ineffectiveness of immunosuppressive therapy in lymphocytic myocarditis: an overview. *Ann Intern Med* 1998;**129**:317–22.
5 **Ciszewski A**, Bilinska ZT, Lubiszewska B, *et al*. Dilated cardiomyopathy in children: clinical course and prognosis. *Pediatr Cardiol* 1994;**15**:121–6.
6 **Balaji S**, Wiles HB, Sens MA, *et al*. Immunosuppressive treatment for myocarditis and borderline myocarditis in children with ventricular ectopic rhythm. *Br Heart J* 1994;**72**(4):354–9.
7 **Kleinert S**, Weitraub RG, Wilkinson JL, *et al*. Myocarditis in children with dilated cardiomyopathy: incidence and outcome after dual therapy immunosuppression. *J Heart Lung Transplant* 1997;**16**:1248–54.
8 **Ino T**, Okubo M, Akimoto K, *et al*. Corticosteroid therapy for ventricular tachycardia in children with silent lymphocytic myocarditis. *J Pediatr* 1995;**126**:304–8.
9 **Ahdoot J**, Galindo A, Alejos JC, *et al*. Use of OKT3 for acute myocarditis in infants and children. *J Heart Lung Transplant* 2000;**19**:1118–21.
10 **Chan KY**, Iwahara M, Benson LN, *et al*. Immunosuppressive therapy in the management of acute myocarditis in children: a clinical trail. *J Am Coll Cardiol* 1991;**17**:458–60.
11 **Lee KJ**, McCrindle BW, Bohn DJ, *et al*. Clinical outcomes of acute myocarditis in childhood. *Heart* 1999;**82**:226–33.
12 **Camargo PR**, Snitcowsky R, da Luz PL, *et al*. Favourable effects of immunosuppressive therapy in children with dilated cardiomyopathy and active myocarditis. *Pediatr Cardiol* 1995;**16**:61–8.
13 **Giulia Gagliardi M**, Bevilacqua M, Bassano C, *et al*. Long term follow up of children with myocarditis treated by immunosuppression and of children with dilated cardiomyopathy. *Heart* 2004;**90**:1167–71.
14 **McMahon AM**, van Doorn C, Burch M, *et al*. Improved outcome for end stage dilated cardiomyopathy in children. *J Thorac Cardiovasc Surg* 2003;**126**:1781–7.
15 **Burch M**, Siddiqi SA, Celermajer DE, *et al*. Dilated cardiomyopathy determinants of outcome. *Br Heart J* 1994;**72**:246–50.
16 **Griffin ML**, Hernandez A, Martin TC, *et al*. Dilated cardiomyopathy in infants and children. *J Am Coll Cardiol* 1988;**11**:139–44.
17 **Tomloka W**. Effects of prednisolone in acute viral myocarditis in mice. *J Am Coll Cardiol* 1986;**4**:868–72.
18 **Shirali GS**, Chinnock RE, Johnson JK, *et al*. Association of viral genome with graft loss in children after cardiac transplantation. *N Engl J Med* 2001;**344**:1498–503.
19 **Kuhl U**, Pauschinger M, Schwimmbeck P, *et al*. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with persistence of viral genomes and left ventricular dysfunction. *Circulation* 2003;**107**:2793–8.
20 **Cooper LT**, Berry GJ, Shabetai R. Idopathic giant cell myocarditis: natural history and treatment. *N Engl J Med* 1997;**336**:1860–6.
21 **Frustaci A**, Chimenti C, Calabrese F, *et al*. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus non-responders. *Circulation* 2003;**107**:857–63.
22 **Liu PP**, Mason JW. Advances in the understanding of myocarditis. *Circulation* 2001;**104**:1076–82.
23 **Gagliardi MG**, Bevilacqua M, Squitieri C, *et al*. Dilated cardiomyopathy caused by acute myocarditis in paediatric patients. *J Heart Lung Transplant* 1993;**12**:S224–9.