Systematic review and meta-analysis

Intravenous immunoglobulin plus corticosteroids prevent coronary artery abnormalities in Kawasaki disease

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Commentary on: **Chen S**, Dong Y, Yin Y, *et al*. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. *Heart* 2013;**99**:76–82.

Context

Kawasaki disease (KD) is a medium vessel vasculitis affecting approximately 8 of 100 000 children under the age of 5 per year in the UK. It is the commonest cause of acquired heart disease in children in developed countries.[1] The cause remains elusive. KD is associated with coronary artery aneurysms (CAA) in over 20% of untreated patients; intravenous immunoglobulin (IVIG) reduces CAA frequency to 5%. Only 2–3% of untreated cases die as a result of coronary vasculitis, and KD is an important cause of long-term cardiac disease in adult life. Patients who do not respond to IVIG are at increased risk of developing CAA. Corticosteroids are an effective treatment for other forms of vasculitis, but early retrospective (and probably biased) analyses suggested that corticosteroids were associated with increased risk of CAA.[2]

Methods

Chen and colleagues report their meta-analysis comparing the frequency of CAA in patients treated with IVIG + corticosteroids or IVIG alone for the primary treatment of KD. They followed standard guidelines for conduct of meta-analyses, and included nine clinical studies involving 1011 patients. Of these, six studies were prospective randomised controlled trials (RCTs); two were non-randomised controlled studies and one was a retrospective report. Of the 1011 patients included, 536 received IVIG + corticosteroids and 475 received IVIG alone.

Findings

Significantly fewer patients receiving IVIG + corticosteroids developed CAA than those receiving IVIG alone (7.6% vs 18.9%, OR 0.30, 95% CI 0.20 to 0.46). The benefit was found in several subgroup analyses. The authors found no significant differences in frequency of severe adverse events between the steroid and non-steroid treatment groups.

Commentary

The present meta-analysis provides convincing evidence that steroids combined with IVIG as initial treatment reduces the overall risk of CAA in severe KD. Clinicians should now consider whether these findings are applicable to their patient population. Heterogeneity in corticosteroid dosing across the trials included is an important consideration. Is it valid to consider a single pulse of high-dose methylprednisolone[3] as equivalent to 4 weeks of prednisolone reported in the Japanese RAISE study,[4] and include these different regimens in a meta-analysis? Moreover, many patients were only included if they were at high risk of IVIG resistance. This meta-analysis may therefore say more about the beneficial effect of steroids in Japanese patients meeting the criteria for predicted IVIG resistance, than about an overall benefit in unselected patients.

So what should clinicians treating KD do in light of the current data? We suggest that corticosteroids should be considered for: (1) patients who have already declared themselves as IVIG resistant; (2) patients with features of the most severe disease (the very young, those with markers of severe inflammation, including: persistently elevated C reactive protein (CRP) despite IVIG, liver dysfunction, hypoalbuminaemia and anaemia) and (3) patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation.

From the studies included, an intravenous preparation equivalent to 2 mg/kg prednisolone for 5–7 days (until

CRP normalises), followed by an oral prednisolone weaning over 2–3 weeks seems logical. Clinicians will need to decide if this should be given in addition to a second dose of IVIG, as some patients not fully responding to the initial dose do respond to a second dose. Vigilance during follow-up for the presence of corticosteroid-related complications is required.

The uncertainties raised by the recent studies can only be answered by well-conducted fully powered randomised trials addressing the issues of patient selection, dose and safety of corticosteroid treatment, as well as use of antitumour necrosis factor α agents. It is time for an international drive to improve the evidence base for treatment of this important childhood disease.

Competing interests None.

References

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