ATG plus cyclosporine reduces all-cause mortality in patients with severe aplastic anemia: systematic review and meta-analysis


CRD summary
The authors concluded that a combination of antithymocyte globulin and cyclosporine reduced short- and long-term mortality in patients with newly diagnosed severe aplastic anaemia compared to antithymocyte globulin alone. Effects on non-severe aplastic anaemia remained unclear. In view of the small number and questionable quality of the included studies, a degree of caution may be advisable in interpreting these findings.

Authors' objectives
To evaluate a combination of antithymocyte globulin (ATG) and cyclosporine (CsA) as first line treatment for aplastic anaemia.

Searching
Canet (Cochrane Cancer Network specialised register of trials), Cochrane Central Register of Controlled Trials, PubMed, meta Register of Controlled Trials and ClinicalTrials.gov were searched for published, unpublished and ongoing studies. Search terms were reported. Search dates varied across sources and spanned 1966 to March 2008. References of eligible studies were handsearched, as were the proceedings of four national and international haematology conferences (2002 to 2008).

Study selection
Randomised controlled trials (RCTs) that compared antithymocyte globulin with cyclosporine versus antithymocyte globulin alone for first-line treatment of newly diagnosed aplastic anaemia were eligible for inclusion. All grades of severity were included: severe aplastic anaemia (SAA); non-severe aplastic anaemia (NSAA); and very severe aplastic anaemia (VSAA). The primary review outcome was all-cause mortality at three months, one year and five years. Secondary outcomes were the proportion of patients with no haematological response and rates of relapse, clonal evolution (acute myeloid leukaemia, myelodysplastic syndrome or paroxysmal nocturnal haemoglobinuria), infection and adverse events.

The age of participants in the included studies ranged from two to 80 years (where reported); median ages were between nine and 36 years. They were diagnosed with idiopathic severe aplastic anaemia or very severe aplastic anaemia and did not meet the criteria for bone marrow transplant. One study included children aged less than 18 years who were recently diagnosed with non-severe aplastic anaemia. One of the adult studies also included a group with non-severe aplastic anaemia. Exclusion criteria varied and included systemic infection, Fanconi anaemia and congenital aplastic anaemia. Where stated, the intervention was horse or pig antithymocyte or antilymphocyte globulin for five days plus cyclosporine for up to a year plus (in most cases) methylprednisolone. Drug doses varied. Controls received regimens without cyclosporine. Definitions for haematological response varied across studies (detailed in the review). Outcomes were assessed on two to four occasions during follow up. Duration of follow up ranged from six months to 14 years.

Studies were selected by two reviewers who worked independently.

Assessment of study quality
The quality of random sequence generation, allocation concealment and blinding procedures was assessed by two reviewers.

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs). Data were extracted by two reviewers. Study authors were contacted for additional information as required.
Methods of synthesis
Studies were grouped by diagnosis (severe aplastic anaemia or non-severe aplastic anaemia). Very severe aplastic anaemia was analysed as a subset of severe aplastic anaemia. Study data were combined to calculate a pooled RR and 95% CI. The number needing treatment (NNT) to prevent one death was reported. The $X^2$ test and $I^2$ statistic were used to assess heterogeneity. Where significant heterogeneity was detected ($p<0.10$ or $I^2>50\%$), the DerSimonian and Laird random-effects model was used; otherwise a Mantel-Haenszel fixed-effect model was used. A study that included both severe aplastic anaemia and non-severe aplastic anaemia data was excluded in sensitivity analysis.

Results of the review
Four RCTs were included in the review (n=313 or 344, text and table inconsistent), two of which were published only as conference abstracts. Two RCTs reported adequate sequence generation and allocation concealment. None reported blinding.

Antithymocyte globulin plus cyclosporine versus antithymocyte globulin alone: Among studies of severe aplastic anaemia and very severe aplastic anaemia, there was a statistically significant reduction in all-cause mortality in the intervention group at three months (RR 0.50, 95% CI 0.29 to 0.85, NNT=8, $p<0.01$; three RCTs, $I^2=0\%$), one year (RR 0.54, 95% CI 0.30, 0.99, NNT=8, $p<0.05$; two RCTs, $I^2=0\%$) and five years (RR 0.58, 95% CI 0.36 to 0.93, NNT=5, $p<0.0003$; three RCTs, $I^2=51\%$). Sensitivity analysis that excluded non-severe aplastic anaemia data increased the effect size at five years (RR 0.46, 95% CI 0.32 to 0.67). There was a statistically significant reduction in the no-response rate in the intervention group (RR 0.53, 95% CI 0.32 to 0.72; three RCTs). No statistically significant difference was found between the two groups for rates of relapse or clonal evolution. There were insufficient data for analysis of adverse events or infection rates.

Studies of non-severe aplastic anaemia found no statistically significant difference between the groups for any outcome; however, data were scarce.

Authors’ conclusions
A combination of antithymocyte globulin and cyclosporine reduced both short-term and long-term mortality in patients with newly diagnosed severe aplastic anaemia compared with antithymocyte globulin alone. Effects on non-severe aplastic anaemia were unclear due to insufficient data.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies. A specific attempt was made to retrieve unpublished studies, but no test for publication bias appeared to be conducted. It was unclear whether the search was restricted by language. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer involved in selection of studies, assessment of validity and data extraction. Some relevant criteria were used to assess study validity, but no details were provided on other important components of validity such as the follow-up rate. The quality of the included studies was suboptimal, even on the basis of the limited validity criteria applied. Appropriate statistical methods were used to combine the data and assess for heterogeneity. However, clinical and methodological heterogeneity between the studies was not discussed and marked inconsistency in one analysis ($I^2=51\%$) was not acknowledged. The authors’ conclusions appeared to reflect the evidence presented, but in view of the small number and questionable quality of the included studies a degree of caution may be advisable in interpreting their findings.

Implications of the review for practice and research
Practice: The authors stated that the combination of antithymocyte globulin and cyclosporine should be regarded as the gold standard for treating patients with severe aplastic anaemia (and possibly also those with very severe aplastic anaemia) who were ineligible for allogeneic transplant. The combined treatment should be promoted by cancer centres.

Research: The authors stated that international multicentre trials were needed to investigate the use of combination immunosuppressants for aplastic anaemia, especially in patients with non-severe disease. They suggested that other research priorities were the optimal treatment of aplastic anaemia in the elderly and the timing and rate of cyclosporine tapering-off.
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