Meta-analysis of CMVIG studies for the prevention and treatment of CMV infection in transplant patients

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Authors' objectives
To evaluate the effectiveness of the immunoglobulin (IG) preparation for cytomegalovirus (CMV) for the prevention and treatment of CMV infection in transplant patients.

Searching
Computerised searches for papers, relevant abstracts, and proceedings were undertaken to identify all articles and abstracts, published between 1982 and 1994, on the use of human hyperimmune globulin enriched for CMVIG antibodies among patients undergoing solid organ and bone marrow transplants.

Study selection
Study designs of evaluations included in the review
Published papers of clinical experience with CMVIG for prevention and treatment of CMV infection. The study designs were either randomised, prospective controlled or retrospective controlled trials.

Specific interventions included in the review
Human hyperimmune globulin enriched for CMVIG antibodies, defined as CMVIG if the report specified it as CMV-specific/hyperimmune and/or as having CMV antibody levels of at least 1:6400 ELISA units/mL. The range of total antibody levels reported was 1:8,000 to 1:64,000 ELISA units/mL; the range of neutralising antibody levels was 1:240 to 1:4,096 ELISA units/mL.

Participants included in the review
Bone marrow and solid organ transplant patients receiving CMVIG as prophylaxis were included.

Outcomes assessed in the review
The three outcomes assessed for the randomised controlled studies were:

the occurrence of CMV infection (primary, reactivation, or superinfection);
the occurrence of severe CMV disease among patients with solid organ or bone marrow transplant who were treated or given prophylaxis; and
death from CMV disease among those receiving CMVIG for prophylaxis and/or treatment of CMV disease.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.[A: The authors reply that all papers found were included in the review.]

Assessment of study quality
No specific criteria were used to assess quality, but randomised studies were evaluated separately from non-randomised studies.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.[A: The authors have added that two of the authors independently extracted the data. The two authors compared the extracted data, discussed disagreements, re-read the papers and reached consensus.]
Methods of synthesis
How were the studies combined?
The pooled odds ratio (OR) estimate was calculated, along with 95% confidence intervals (CIs), using the Mantel-Haenszel fixed-effect model. The same model was also used to calculate p-values.

How were differences between studies investigated?
[A: The authors state that differences between studies were assessed qualitatively by the authors.]

Results of the review
Twenty-three studies with 295 bone marrow and 321 solid organ transplant participants were included. Twelve papers were randomised controlled trials and one study was blinded. In the statistical analysis, for each of the three study outcomes, the sample size was the total number of patients in each study that reported the specific outcome.

In all studies (14) on prophylaxis for CMV infection, there were 377 patients in the CMVIG group (128 from non-randomised studies and 98 from randomised studies) and 447 in the control group (207 from non-randomised studies and 240 from randomised studies). Prophylaxis for CMV infection was statistically significant (pooled OR 0.56, 95% CI: 0.41, 0.77). In only the randomised studies, prophylaxis for CMV infection was also statistically significant (pooled OR 0.56, 95% CI: 0.37, 0.84).

In all studies (14) on the prevention of severe CMV disease or CMV pneumonia, there were 519 patients in the CMVIG group (209 from non-randomised studies and 310 from randomised studies) and 512 in the control group (222 from non-randomised studies and 290 from randomised studies). Prevention of severe CMV disease or CMV pneumonia was statistically significant (pooled OR 0.59, 95% CI: 0.40, 0.86), and was also significant in only the randomised studies, (pooled OR 0.47, 95% CI: 0.29, 0.76).

In all studies (14) on the prevention of CMV death, there were 478 patients in the CMVIG group (244 from non-randomised studies and 234 from randomised studies) and 615 in the control group (366 from non-randomised studies and 249 from randomised studies). Prevention of CMV death was statistically significant (pooled OR 0.26, 95% CI: 0.15, 0.45), and was also significant in only the randomised studies (pooled OR 0.34, 95% CI: 0.18, 0.62).

Authors’ conclusions
The consistency of the results across the 23 studies indicated the effectiveness of CMVIG in the prevention and treatment of CMV infection among patients undergoing transplant.

CRD commentary
The authors conducted a reasonable review. The review’s strengths lie in the presentation of the data from the original studies, the statistical pooling of the data, and the data analysis. Its main weaknesses are found in the lack of transparency in the process of selection, evaluation, and data extraction for the original studies.

The authors did not specify which databases were searched, and did not report whether non-English language articles and abstracts or unpublished data were included. Therefore, it is unclear whether additional relevant studies may have been missed. The authors’ statement that all published literature was located cannot, therefore, be supported.

The inclusion criteria for the individual trials and their participants were stated but, with the exception of the distinction between randomised and non-randomised controlled trials, the quality of the included studies was not assessed.

The authors tested for heterogeneity but these results were not reported.

Comparing the results for all studies versus those for randomised studies, very little difference in ORs was reported. However, the results of the non-randomised studies may have been biased in favour of a reported benefit by participants, because those case series were retrospective in design.
The authors’ conclusions follow from the results reported but these should be viewed with some caution because of the mixing of study designs, and the possibilities of bias in the processes of study selection, inclusion, and data extraction.

**Implications of the review for practice and research**

Practice: The authors’ conclusions state that CMVIG is effective in the prevention and treatment of CMV infection in practice.

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

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