Studies evaluating high-dose acyclovir, intravenous immune globulin, and cytomegalovirus hyperimmunoglobulin for prophylaxis against cytomegalovirus in kidney transplant recipients

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Authors' objectives
To critically analyse the studies evaluating the cost, safety, and efficacy of high-dose acyclovir, intravenous immunoglobulin (IVIG) and cyclomegalovirus hyperimmunoglobulin (CMVIG) for prophylaxis against CMV in kidney transplant recipients.

Searching
MEDLINE was searched using combinations of the following MeSH: 'immunoglobulins', 'intravenous' 'acyclovir' 'CMVIG' 'CMV infections' 'kidney transplantation' 'IVIG' and 'prophylaxis'.

Study selection
Study designs of evaluations included in the review
The included studies were of randomised controlled trials (RCTs), open-label uncontrolled trials, open-label non-randomised controlled, non-randomised uncontrolled, and non-randomised controlled and retrospective open-label uncontrolled non-randomised trials that evaluated or discussed the cost, safety, and efficacy of IVIG, high-dose acyclovir, and CMVIG in kidney transplant recipients. The studies included and assessed the effect of the stated treatment regime with a placebo control group, without a placebo control group, or with immunoglobulin G as a control.

Specific interventions included in the review
Prophylactic treatment was given before and after transplant with the following regimes: acyclovir to patients on immunosuppressive regimes including prednisolone, azathioprine, cyclosporin and antilymphocyte globulin; IVIG with or without ganciclovir to patients on immunosuppressive regimes including prednisolone, azathioprine, cyclosporin, OKT3 and antilymphocyte globulin; CMVIG) to patients on various immunosuppressive regimes including prednisolone, azathioprine, cyclosporin and antilymphocyte globulin.

Participants included in the review
Patients having a kidney transplant. Patients were recipients of cadaver and living donors with a mix of donor and recipient CMV serology.

Outcomes assessed in the review
The main outcomes were: CMV infection, defined as the presence of CMV antibodies in a previously CMV-seronegative patient or a 4-fold rise in antibody titre after transplantation; CMV syndrome, defined as CMV infection plus unexplained fever, leucopenia or thrombocytopenia in the absence of an identifiable cause; CMV disease, defined as CMV syndrome plus pneumonitis, enteritis, retinitis, hepatitis or central nervous system involvement.

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.

Assessment of study quality
The studies were evaluated with respect to study design, patient population, and investigators' definitions of terminology. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.
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.

Methods of synthesis
How were the studies combined?
The studies were combined by a narrative review.

How were differences between studies investigated?
The possible causes of differences between the studies were discussed.

Results of the review
Acyclovir: 1 RCT (104 patients), 1 open-label uncontrolled trial (12 patients) and 1 non-randomised uncontrolled trial (14 patients).

IVIG: 3 RCTs (113 patients), 1 open-label non-randomised control trial (56 patients), 1 non-randomised trial with concurrent controls (18 patients), and 1 non-randomised trial with historical controls (11 patients).

CMVIG: 1 RCT (59 patients) with a no-treatment control, 2 RCTs (87 patients) with control group receiving immunoglobulin, 1 non-randomised controlled trial (36 patients), and 1 non-randomised uncontrolled trial (174 patients). One of the RCTs (59 patients) was used to evaluate CMV syndrome.

Results were reported for individual studies. Only the treatment effects from the RCTs are reported below.

Acyclovir (1 RCT): CMV infection, 31% in treatment group compared to 61% in placebo (p=0.01); CMV syndrome, 7.5% in treatment group compared to 29% in the placebo group (p=0.002); CMV disease, 2% in treatment group compared to 17% in the placebo group (p=0.017).

IVIG: the results are not consistent but the incidence of CMV syndrome in the treatment group tended to be equal to or lower than that in the control group. CMVIG versus control (1 RCT): CMV syndrome, 21% in CMVIG and 60% in the control group (p<0.01); CMV disease, 13% in CMVIG and 46% in the control group (p<0.01).

CMVIG versus IVIG (2 RCTs): CMV syndrome, 0 versus 71% in one study and results not reported in the other.

Cost information
The average wholesale cost of each regime was estimated at: US$1,243 for acyclovir, $6,930 for CMVIG and $5,880 for IVIG. IVIG therapy was costed in three studies; these suggested a saving of $3,300 per patient in the cost of hospitalisation for patients receiving treatment. An estimate of $29,800 per life saved was made for CMVIG therapy in the highest-risk groups. This rose to $1.68 million per life saved in the lowest-risk groups.

Authors' conclusions
High-dose acyclovir, IVIG and CMVIG effectively reduce the incidence of CMV-associated complications in kidney transplants by varying degrees. The most effective prophylactic treatment is unknown because of the lack of well-designed trials comparing costs, efficacy and safety. More studies are necessary before the safest, most efficacious and most cost-effective regime can be identified.

CRD commentary
The literature search was limited to one database. A more extensive search may have revealed other relevant studies. The studies were not formally evaluated for quality and many of the studies were of small size. As correctly stated by the author, the studies suffer from differences in terminology, duration of prophylaxis, immunosuppressive regimes, methodology, patient populations, CMV titres of IVIG products, absence of prospective criteria to monitor adverse
reactions, and mixed donor and recipient serology. The latter is of particular relevance since the donor-recipient serology mix affects the risk of the recipient, yet it does not appear to have been accounted for in the analysis of the individual studies. A more appropriate strategy may have been to extend the literature search and select only those studies of higher quality than a predefined minimum. CMV disease is stated by the author to usually appear 2 to 6 months after transplant but no details are given of the follow-up period of any of the studies. If the study period were shorter than 6 months an underestimate of CMV-associated disease would result.

**Implications of the review for practice and research**
Good quality studies are required before the safest, most efficacious and most cost-effective regime can be identified.

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