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**OPTIMAL GANCICLOVIR PROPHYLAXIS STRATEGIES TO PREVENT CYTOMEGALOVIRUS REACTIVATION DURING BACTERIAL SEPSIS**

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**Introduction:** It has been confirmed by numerous investigators that previously immunocompetent critically ill patients can reactivate latent cytomegalovirus (CMV), and that reactivation is associated with significantly higher morbidity and mortality. Using our murine model, we have shown that sepsis can trigger CMV reactivation, and that sepsis-induced reactivation can be prevented with ganciclovir (GCV) (10mg/kg/day x 21). It has been suggested that therapeutic trials in humans be done to confirm a cause/effect relationship, and we therefore sought to determine an optimal GCV treatment strategy.

**Methods:** BALB/c mice latently infected with murine CMV (MCMV) were subjected to cecal ligation and puncture and randomized to one of five treatment groups. Seventy-one surviving mice received either therapeutic GCV (10 mg/kg/day x 21 days, n=12), short course therapeutic GCV (10 mg/kg/day x 7, n=16), low-dose GCV (5 mg/kg/day x 21, n=14), delayed therapeutic GCV (10 mg/kg/day x14, delayed 7 days, n=14), or saline (n=15). Short course GCV and low-dose regimens limit GCV exposure during prophylaxis, while delayed GCV simulates treatment after diagnosis. Pulmonary reactivation was determined by examined by RT-PCR for MCMV mRNA, and histologic sections were evaluated for tissue fibrosis. In separate experiments, the influence of GCV on early LPS induced pulmonary TNF expression was studied by quantitative PCR 1, 3, & 7 days after treatment.

**Results:** There was no significant difference in sepsis survival between treatment groups (~60%), and all GCV treatment regimens prevented MCMV reactivation significantly better than saline ( $p<0.002$ ). "Therapeutic" GCV had the lowest incidence of reactivation (1/12), and short-course GCV therapy showed similar reactivation (2/16). Both low dose and delayed GCV were associated with significant breakthrough reactivation (6/14 and 7/14 respectively). "Therapeutic" GCV was associated with the lowest incidence of pulmonary fibrosis, and importantly all other regimens showed similar fibrosis to saline treatment. Delay of therapy for 1 week after sepsis onset was associated with significantly worse pulmonary fibrosis ( $p<0.05$ ) than early therapy. GCV therapy did not seem to influence TNF expression early after sepsis.

**Conclusion:** Although short-course therapeutic GCV is very efficacious at preventing reactivation after sepsis, it is unclear that short-course therapy will prevent pulmonary injury or inflammation. Delay of therapy for 1 week is associated with ~50% CMV reactivation, and pulmonary injury similar to no therapy at all. These results suggest that a treatment trial in humans should use therapeutic doses administered as early as possible to minimize reactivation and associated pulmonary injury.