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Gamma Interferon Supplementation for Melioidosis

Mortality from melioidosis approaches 50% despite appropriate antimicrobial therapy (4), and new approaches are urgently needed. *Burkholderia pseudomallei* is an intracellular pathogen, and gamma interferon (IFN-γ)-mediated responses are essential for the normal host response to melioidosis (7). Plasma levels of IFN-γ are already high in patients with acute melioidosis (2), but it is tempting to speculate that a relative IFN-γ deficiency exists. The finding by Propst et al. that IFN-γ supplementation confers a survival benefit in murine melioidosis (6) is exciting, as there already exists an FDA-licensed preparation of IFN-γ (Actimmune, InterMune Inc.; >$300/dose). The up-front cost is high, but this was not a barrier to evaluating granulocyte colony-stimulating factor (G-CSF) in a clinical trial (1). We are therefore motivated to outline two issues that remain to be addressed before IFN-γ supplementation can be transferred from bench to bedside.

In the mouse experiments, the investigators deliberately selected a subtherapeutic ceftazidime dose (50 mg/kg of body weight/day) when a more appropriate dose might be 1,200 mg/kg/day (5). While we agree with the authors' sentiment that "full-dose therapy should be capable of generating even greater protection," the clinical question is whether IFN-γ supplementation might improve survival when combined with the current recommended antimicrobial therapy, and there is no clinical situation in which low-dose ceftazidime would be used. Had full-dose ceftazidime been used, it is possible that the bacterial burden may have been so reduced by ceftazidime alone that no additional effect would be seen with supplemental IFN-γ. When contemplating a clinical trial of IFN-γ therapy, we would prefer to see first evidence from studies using full-dose ceftazidime, and it would be reassuring to hear from the authors that these studies are in progress. Should no effect be seen on mortality (e.g., because all mice survive), then differences in bacterial clearance rates would still be relevant, because the median fever clearance time in patients with melioidosis is 9 days despite ceftazidime, and intravenous antimicrobial therapy must sometimes be continued for >1 month.

The issue of diagnosis could not have been addressed by this study but relates directly to the clinical implementation of IFN-γ therapy. Acute melioidosis has no clinical features that allow it to be reliably distinguished from other causes of severe sepsis, except isolation of *B. pseudomallei*, which means a delay of 24 to 48 h. Around half the patients with melioidosis die within 48 h of presentation, so therapy is often begun on clinical suspicion alone (4). The result is that less than half of all patients treated empirically for melioidosis have culture confirmation of their disease (8). IFN-γ supplementation started prior to microbiological confirmation inevitably means the inadvertent treatment of other infections. Aside from an added financial burden, the effect of IFN-γ supplementation in other causes of sepsis is unclear. In a murine model of polymicrobial sepsis, IFN-γ supplementation increased mortality in a dose-dependent fashion (3), which means that pending improvements in the diagnosis of melioidosis, any benefit of IFN-γ supplementation may be negated by a deleterious effect of IFN-γ on other causes of community-acquired sepsis.

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Author's Reply

We appreciate the comments by Koh regarding our recently published study (1) and the clinical relevance of our findings that treatment with IFN-γ increased the effectiveness of antimicrobial therapy for acute melioidosis. We agree that the use of a subtherapeutic dose of ceftazidime to explore the effectiveness of IFN-γ in enhancing bacterial clearance and survival in our acute pulmonary challenge model begs the question of whether combination therapy would be effective at therapeutic antibiotic doses. Therefore, experiments are under way in our lab to investigate the interaction between conventional high-dose ceftazidime therapy and immunotherapy, using much higher bacterial challenge doses than were employed in our original studies.

Regarding the issue of a delay in diagnosis of melioidosis and the possible adverse effects of IFN-γ when administered to septic patients, we again agree with this concern, though we also point out that the literature is not clear regarding whether IFN-γ is helpful or harmful in sepsis (e.g., reference 2). However, we believe that the greater impact of combined immune and antimicrobial therapy is likely to be realized in the treat-

ment of chronic *B. pseudomallei* infection, where IFN-γ could be of significant benefit in increasing the effectiveness of antimicrobial therapy in eradicating reservoirs of persistent infection. For example, we note that in our report, *B. pseudomallei* infection was completely eradicated in a significant number of animals treated with only a very short course of immunotherapy and antimicrobial therapy.

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