Reviewer’s report

Title: Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series

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Reviewer: Sunil Shaunak

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This paper by Delsing et al describes the studies in 8 patients with life threatening invasive fungal infections who were treated with recombinant interferon-gamma (100 µg subcutaneously 3 times weekly) for only 2 weeks (i.e., 6 doses) in addition to standard antifungal therapy.

Comments on the clinical data set:

The important clinical observation is that 6 of the 8 patients treated with just a 6 doses of interferon-gamma over 2 weeks recovered from their fungal infection. The other two patients were already in the intensive care unit and were therefore likely to have been so critically ill at the time that interferon-gamma treatment was initiated that this therapeutic intervention was too late for them – this probably explains why they died. Given that this group of very sick patients is so difficult to study, the clinical outcome data is important enough to justify its publication.

I agree with the authors that a multicentre trial is now needed to fully explore and to define the therapeutic efficacy of interferon-gamma immunotherapy in life threatening invasive fungal infections.

I cannot see that Figure 1 adds anything useful to the information that could easily and succinctly be summarised in the paper’s text.

I cannot see that Figure 5 adds anything useful to information that could also be easily and succinctly summarised in the paper’s text.

Figure 7 is a useful albeit brief summary. It would benefit from referring only to the patient clinical details. In my opinion, it is not useful to provide the baseline TNF-alpha or the baseline HLA-DR data in this figure.

Comments on the in-vitro studies data set:

The authors suggest that the most important observation is the increase in HLA-DR expression on blood monocytes with interferon gamma therapy. It is not clear to me how the percentage calculation on the y-axis of Figure 6 has been determined. This should be clarified. In addition, they refer to a paper by Meisel et al in 2009 (reference 30) to justify their splitting of the interferon gamma treated patients into those with <50% HLA-DR expression (and then defined as immuno-paralysed) and those with >50% HLA-DR expression (and then defined
as immuno-competent.). I cannot find any reference in the Meisel et al (2009) paper which justifies using such a cut-off to draw Figure 6. The authors need to provide more clarification about this matter.

Figures 2, 3 and 4 relate to in-vitro stimulation of PBMCs from interferon gamma treated patients with a variety of exogenous ligands. It is not clear to me why the stimulation assays for IL-1 beta and TNF-alpha were performed for 24 hours only, whilst the stimulation assay for IL-17 and IL-22 were performed for 7 days, and the stimulation assay for IL-10 was then performed for 2 days. The reasons for this need to be explained in full by the authors.

With regard to their interpretation of the results as shown in Figures 2, 3 and 4, the authors state that there are increased ex-vivo responses for IL-1 beta and TNF-alpha, as well as for IL-17 and IL-22. My reading of the graphs leads me to conclude that increases in IL-1 beta and TNF-alpha are only seen on days 1 and 2 after starting interferon gamma therapy. In the case of IL-17 and IL-22, an increase is only seen on day 1 after starting interferon gamma therapy.

I am concerned that the authors have over-interpreted the data as shown in Figures 2, 3 and 4 as currently shown in the manuscript.

The authors conclude with the following sentence “Biomarkers of impaired anti-fungal immunity should be described in order to identify patients who will benefit most from immuno-stimulatory therapy”. I would refer the authors of the paper of Armstrong-James et al entitled “Renal allograft recipients fail to increase interferon gamma during invasive fungal diseases” that was published as a brief communication in the Amer J Transplantation (2012; 12: 3437 -40). A blood based assay is described in this paper which could be used to identify those patients who could benefit from interferon gamma therapy. The authors should reference this paper at the end of their discussion.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

None.