Response to: 'Correspondence to: 'Combination of human umbilical cord mesenchymal stem cell transplantation with IFN-γ treatment synergistically improves the clinical outcomes of patients with rheumatoid arthritis" by Ma *et al*

We thank Ma *et al*[1] for their interest in our recent report titled 'Combination of human umbilical cord mesenchymal stem (stromal) cell transplantation with IFN-γ treatment synergistically improves the clinical outcomes of patients with rheumatoid arthritis'.[2] Ma *et al*[1] brought up an important issue regarding the safety profile of intramuscular infusion of interferon (IFN)-γ, which may initiate further immune reactions.[3 4] As previously described, recombinant human IFN-γ monotherapy is known to be safe but ineffective in treating rheumatoid arthritis.[5 6] Furthermore, the safety of IFN-γ-primed mesenchymal stem (stromal) cells (MSCs) remains unknown, as there has been no such clinical research report addressing this issue. Therefore, for the subject's maximum safety considerations, the clinical protocol was MSC transplantation (MSCT) plus intramuscular infusion of IFN-γ, instead of IFN-γ-primed MSCs, and as we have anticipated no new or unexpected safety issues were reported for either treatment group for up to 1 year. Indeed, in future studies, interpreting the safety of the IFN-γ-primed MSC protocols would be more appropriate than that of recombinant IFN-γ monotherapy from a translational standpoint.

As to the question of whether MSCT plus intramuscular infusion of IFN-γ would further modulate serum levels of IFN-γ in patients, all patients who received intramuscular infusion of IFN-γ had a transient increase in serum IFN-γ level within 24 hours after infusion, which gradually decreased during the subsequent follow-up. However, as we described in our previous study that there are huge individual variations in the baseline serum IFN-γ levels,[7] we did not list the IFN-γ data. In addition, with regard to the serum level of proinflammatory cytokines, consistent with our previous study,[7] there was a significant decrease in the serum levels of tumour necrosis factor-α and interleukin (IL)-6 among patients of the MSCT plus IFN-γ group, while no significant changes in IL-1β, IL-2R and IL-8 levels were observed. Unfortunately, we did not find that such a proinflammatory cytokine combination affected the immunosuppressive functions of MSCs, as observed in the in vitro study.

Finally, we agreed that it is possible that the flow cytometry (FC) gauged percentages of CD3+ and IFN-γ+ MSCs could differ using different control techniques for gating. In our study, isotype controls were used for identification of the background binding caused by antibody isotypes. As there are only two kinds of fluorochromes involved in the FC experiment, a single positive control technique was more adequate as a compensation control technique than the fluorescence minus one control technique, which is suitable for multiple fluorochromes (≥3) FC study.[8 9]

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