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Letter to the Editor

Mesenchymal Stem Cells Combined with Cyclosporine Inhibits Cytotoxic T Cells

Maccario and collaborators reported that mesenchymal stem cells (MSCs) and cyclosporine had a synergistic effect by inhibiting cytotoxic T-cell lysis of target cells, a finding that may have clinical implications [1]. This effect may explain some of the findings we have seen in our patients who were treated for therapy-resistant graft-versus-host disease (GVHD). In theory, we expected MSCs to have only immunologic effects by inhibiting the afferent phase of alloreactivity and not the efferent phase, because MSCs inhibited mixed lymphocyte cultures (MLCs) and the development of cytotoxic T cells, but not cytotoxicity by already developed cytotoxic T cells [2]. In a boy who was treated for therapy-resistant, acute, grade IV GVHD and responded to MSCs, GVHD occurred when cyclosporine A (CsA) was discontinued after minimal residual disease was detected in a bone marrow aspirate, and we wanted to allow for a maximum graft-versus-leukemia effect [3]. However, he responded promptly by reversal of severe GVHD of the gut and liver a second time when CsA and MSC were reinstituted.

In our further experience of treating therapy-resistant GVHD, we found that, although most patients have had dramatic responses, some do not respond to MSC therapy [4]. Thus, our plan for patients who do not respond to MSC has been to add anti–interleukin-2 receptor antibodies or anti–T-cell globulin to combine MSCs with antibodies directed against cytotoxic T cells. However, in light of the findings of Maccario et al [1], this appears to be unnecessary. Instead, it may be dangerous to treat patients with additional immunosuppressive agents, because MSCs inhibit T-cell responses not only to alloantigens and mitogens but also to infectious agents in vitro. We have also seen that some patients treated with MSCs for severe GVHD have developed severe infectious complications such as disseminating cytomegalovirus, varicella-zoster virus, adenovirus, and *Aspergillus* and *Fusarium* infections [4]. In a patient who underwent a third transplantation due to previous rejections, MSCs were given because of therapy-resistant, extensive, chronic GVHD [4]. Subsequently, this patient developed a gastrointestinal Epstein-Barr virus (EBV) lymphoproliferative disorder that did not respond to repeated treatment with EBV-specific cytotoxic T cells [5]. The reason for this unresponsiveness may have been the synergistic effect of MSCs and CsA on EBV-specific cytotoxic T cells. The synergistic effect between MSCs and CsA on cytotoxic T cells is beneficial in the context of alloreactivity, such as GVHD, but may be deleterious during a concurrent viral infection in a severely immunocompromised patient.

We examined the synergistic effect of MSCs and CsA in lymphocytes stimulated by phytohemagglutinin (PHA) [6]. After lymphocyte stimulation with PHA, MSCs and CsA alone inhibited proliferation; when combined, there was an additive effect. This is in contrast to the synergistic immunosuppressive effect of MSCs and CsA observed in MLCs by Maccario et al [1]. However, we found that MSCs inhibit lymphocyte proliferation by PHA and by alloantigens by different immunologic mechanisms [7]. Thus, MSCs increased levels of interleukin-2 and soluble interleukin-2 receptor in mixed lymphocyte cultures, whereas levels decreased in PHA-stimulated lymphocytes. Interleukin-10 levels increased in MLCs cocultured with MSCs but were not affected in PHA-stimulated lymphocytes. Further, prostaglandins were important in inhibition by MSCs when lymphocytes were stimulated by PHA but not by alloantigens. Thus, studies performed on alloantigen stimulation, such as the studies performed by Maccario et al, may be more clinically relevant to patients who have received transplants than studies on lymphocytes activated by PHA and other artificial mitogens. The findings of Maccario et al suggest that, if MSCs are to be used for treatment of various immunologic disorders, they should be combined with CsA to have an effect where cytotoxic T cells are involved.

In conclusion, the finding of synergy between MSCs and CsA regarding cytotoxic T cells on allogeneic targets has importance for future strategies of how to use MSCs in the clinic.

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