Do mesenchymal stromal cells promote HLA specific antibodies formation after infusion in liver transplant recipient?

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Introduction

Due to their immunomodulatory properties, mesenchymal stromal cells (MSC) could be a means to establish tolerance in solid organ transplantation. Nevertheless, MSC immunogenicity is debated. Some suggested that MSC could up-regulate HLA class I and II on their surface in inflammatory conditions and thus have an “antigen presenting cell functions” which could then theoretically promote specific antibodies formation and graft rejection. These data encourage caution in the clinical use of these cells. We recently published a prospective, controlled, phase I study evaluating a single administration of third-party MSC in 10 liver transplant recipients (LTR). Here, we focus on the development of antibodies (Ab) against MSC-donor HLA (MSC-DSA) in LTR following MSC infusion.

Objectives

- Analyze the appearance of HLA Ab in the follow-up of 10 LTR who received a single administration of third-party MSC compared with a control group of 10 LTR
- Analyze the appearance of specific Ab against MSC-donor HLA in LTR following MSC infusion.

Methods

Ten liver transplant recipients under standard immunosuppression received 1.5–3 $10^6$/kg third-party unrelated MSCs on postoperative day 3 ± 2, and were prospectively compared to a control group of ten liver transplant recipients. Each recipient was genotyped for HLA A/B/C/DR/DQ as well as each liver and MSC donor. Every recipients were tested for HLA Ab before the transplantation and then at month 1, 3 and 6 by the LumineX® technique. Ab were considered as positive in case of MFI >1500 and in accordance with the manufacturer’s recommendations.

Results

In the MSC-treated group, 2 patients (P3 and P8) were sensitized pre-transplant with presence of MSC-DSA. At month-1 after the transplant, 6 more LTR (P1, P2, P4, P7, P9, P10) showed MSC-DSA appearance (against 1 to 2 HLA maximum). Three had still MSC-DSA at month-6 (P1, P7, P9). Among the 6 LTR who developed de novo MSC-DSA, 5 had received multiple red blood cells (RBC) allo-transfusion (P1, P4, P7, P8, P9, P10) and 1 received 1 pool of platelet (P2) before or in the month following transplantation. Those six patients also showed multiple HLA Ab (“others” in the chart) against 5 to 32 different HLA antigens. Seven LTR developed de novo liver DSA in this group. Two LTR didn’t develop any MSC-DSA (P5 and P6) throughout the follow-up. P6 didn’t receive any RBC allo-transfusion.

In the control group, we observed that 2 LTR were sensitized pre-transplant with presence of multiple HLA Ab. Six LTR developed de novo multiple HLA Ab after the transplant with 3 of them developing de novo liver DSA.

Conclusions

In the large pool of HLA Ab identified in LTR post transplant, the detection of MSC-DSA is most likely caused by allo-transfusions rather than related to MSC infusion. The comparison of these results with the histological and clinical impact in LTR has still to be analyzed in this study. Further studies are required to confirm that MSC are “immune privileged”.

References

1. Infusion of third-party mesenchymal stromal cells after liver transplantation: a phase 1, open-label, clinical study. Detry O et al. J Hepatol, 2017
2. Marigo I et al. The immunomodulatory properties of mesenchymal stem cells. Semin Immunopathol, 2011