

# 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

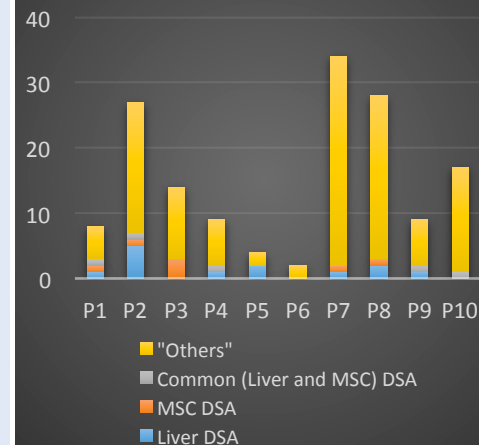
Ten liver transplant recipients under standard immunosuppression received 1.5–3  $10^6$ /kg third-party unrelated MSCs on postoperative day  $3 \pm 2$ , and were prospectively compared to a control group of ten liver transplant recipients. Each recipient was genotyped for HLA A/B/C/DR/DQ as well as each 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  $_{MSC}DSA$ . 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 multiple HLA Ab. Six LTR developed *de novo* multiple HLA Ab after the transplant with 3 of them developing *de novo*  $_{liver}DSA$ .

HLA antibodies in MSC-treated group



## 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

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