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Response to Comment on: "HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial"

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Response to Comment on: "HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial"

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We thank the Editor for the opportunity to respond to the Comment " de Montalembert and Frangoul, Risks and benefits of gene therapy and transplantation in sickle cell disease," regarding our article, "HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial" (Haematologica, XXXXXXX)[1]. Their Comment provides an opportunity to clarify several aspects of our discussion on haploidentical transplantation and gene therapy in sickle cell disease (SCD). Most of the issues they raise do not directly relate to the results of our study but rather to their interpretation of published data on gene therapy for SCD [2,3].

One point raised during our discussion concerns the feasibility of the gene therapy approach. We acknowledge that the following statement may have been misleading: "In addition, the process is more complex, with a higher risk of manufacturing failure: in a recent report, 24% of mobilized patients did not receive exa-cel gene therapy." Our intention was to refer more broadly to the overall feasibility of the procedure. In the study by Frangoul et al, 11 of 58 patients discontinued the process after initiation of stem-cell mobilization and therefore did not proceed to gene therapy [3]. This finding highlights the challenges associated with the mobilization and collection phase, which represents a critical step in the gene therapy pathway. Unfortunately, the publication does not provide detailed information on mobilization outcomes, such as the number of plerixafor mobilization cycles and CD34+ cell yields per collection, in these 11 patients. Nevertheless, these data suggest that stem-cell mobilization remains a limiting factor for a substantial proportion of patients and should be considered when evaluating the real-world feasibility of gene therapy approaches. In addition, Montalembert and Frangoul reported inadequate cell collection in 6 of the 63 enrolled patients (9.5%). However, only 58 patients had initiated stem-cell mobilization, and 3 of these had not yet been dosed at the time of reporting. Evaluating collection outcomes among the 55 patients who had completed mobilization and collection may therefore provide a more accurate assessment of collection success[3].

De Montalembert and Frangoul cite the study by Leonard et al regarding acute pain episodes following hematopoietic stem cell transplantation [5]. Although transplantation resulted in a marked reduction in pain burden compared with the pre-transplant period, pain episodes persisted in a subset of patients and progressively decreased over time. In our experience, pain episodes are also commonly observed during the first months following successful transplantation despite complete biological correction of the sickle cell phenotype (personal data, REDAC meeting 2026). These observations highlight the complexity of pain in SCD, which cannot be entirely attributed to vaso-occlusion. They also illustrate the limitations of using pain as a primary efficacy endpoint and underscore the importance of appropriate control groups when evaluating emerging curative approaches, including gene therapy.

A major issue also concerns the relevance of comparing outcomes between haploidentical transplantation and gene therapy. In allogeneic transplantation, donor chimerism and HbS levels provide robust markers of engraftment, donor-derived erythropoiesis and disease correction, whereas biological efficacy after gene therapy relies on different parameters. Consequently, graft rejection and

event-free survival cannot be directly compared across studies because endpoints differ substantially. In addition, differences in eligibility criteria and patient characteristics further limit cross-trial comparisons. Meaningful comparisons between these therapeutic strategies would require harmonized inclusion criteria, standardized outcome definitions, and similar follow-up assessments.

With regard to the comment on hemolysis, we agree that gene therapy results in major improvements in hemoglobin levels and hemolytic parameters. However, complete normalization does not appear to be achieved in all patients. Mean LDH values remained close to the upper limit of normal during follow up, while mean reticulocyte counts and indirect bilirubin levels remained above normal physiological values (Ref2 Figure S4 and table S8). Furthermore, the wide ranges observed for these parameters suggest heterogeneity in treatment response, with some patients continuing to display laboratory features consistent with residual hemolysis [3].

Finally, we welcome the remarkable progress achieved in both gene therapy and haploidentical transplantation. These approaches should be viewed as complementary rather than competing options for patients with severe SCD lacking an HLA-identical donor. In this context, we echo the recent comments by Pinto et al, published in Haematologica in response to our article, highlighting the importance of independent academic research alongside industry-sponsored trials to generate unbiased data and long-term clinical evidence[6]. Such efforts will be essential to define the optimal place of each strategy and, ultimately, to improve outcomes for patients with SCD.

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