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Risks and benefits of gene therapy and transplantation in sickle cell disease. 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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Dhédin et al. report the results from the phase II DREP-HAPLO experience of haploidentical hematopoietic stem-cell transplant (HSCT) in severe sickle cell disease (SCD)[1]. We welcome the authors' focus on curative intent for SCD and their contributions to study alternative treatment options to serve all patients in need of potentially curative therapies and note the comment from Pinto and Angelucci[2]. To support accurate interpretation, we offer clarifications that reflect recent evidence from exa-cel clinical trials and provide further context so readers can weigh benefits and risks accordingly.

Exa-cel is a cellular therapy consisting of autologous CD34+ hematopoietic stem cells (HSCs) genetically modified by CRISPR/Cas9 to downregulate *BCL11A* expression and increase fetal hemoglobin (HbF) levels[3]. Exa-cel has received approval from eight regulatory agencies worldwide including the FDA, EMA, SFDA, and MHRA, with defined indications (the treatment of severe SCD and transfusion-dependent thalassemia), risk management plan, and post authorization long-term follow-up[4].

Dhédin et al. reports that 24% of patients who underwent stem-cell mobilization in the exa-cel study did not receive exa-cel due to manufacturing failure. Data from the CLIMB-121 trial [3] reports that 10.3% (6 out of 58 patients with SCD who started mobilization) had discontinued due to either inadequate cell collection (3/58) or manufacturing issues (3/58), which is 9.5% (6/63) of all patients enrolled. Evolving evidence on mobilization practices and continuous improvements in manufacturing processes are expected to help overcome known challenges with mobilization in SCD.

Previously published data showed exa-cel eliminated vaso-occlusive crises (VOC) in 97% of patients with severe SCD for a period of 12 consecutive months or more with a mean duration of VOC freedom of 22.4 months (range 14.8 -45.5)[3]. Dhédin et al.[1] did not report on pain episodes post treatment, but we note previous data showing acute pain episodes are known to occur post allo-transplant, including haploidentical HSCT[5]. Post exa-cel, all patients with SCD (100%) were free from hospitalization for VOC for at least 12 consecutive months. Treatment with exa-cel resulted in early, clinically meaningful, and durable increases in HbF with pancellular distribution resulting in total hemoglobin levels at normal or near normal levels. An increase in HbF to >40% was seen from month 6 post exa-cel infusion, above the levels previously shown to be protective in persons with hereditary persistence of fetal hemoglobin and SCD[3].

Hemolysis is central to SCD pathophysiology, and intravascular hemolysis is linked to major complications and excess mortality[6]. Dhédin et al. states that hemolysis persists in about 50% of cases after exa-cel. More detailed review of the published data from the CLIMB-SCD-

121 trial shows clinically meaningful improvements in hemolysis maintained over time[3]. Haptoglobin, a sensitive measure of intravascular hemolysis, which is normally undetectable in people with SCD, increased to detectable levels in all patients after month 6[3]. Mean lactate dehydrogenase (LDH), an additional measure of intravascular hemolysis, decreased from 474.3±200.3 U per Liter at baseline down to levels within the normal range (239.2±145.3 U per Liter) by month 9 post exa-cel treatment and were generally maintained within the normal range over time. These data support clinically meaningful improvements in intravascular hemolysis after exa-cel.

We agree with Dhédin et al. that an advantage of autologous gene therapy, including exa-cel, is the absence of GVHD, therefore GVHD prophylaxis is not required. In this phase 2 trial following haploidentical HSCT, the incidence of acute GVHD grades II-IV was 40.9% and of chronic GVHD was 36% with the majority (27%) at 2-year having moderate-to-severe chronic GVHD. Although most cases resolved (4 out of 6) at last follow-up, chronic GVHD is a debilitating disease that requires chronic immune suppression. Moreover, in CLIMB-SCD-121, all patients achieved neutrophil and platelet engraftment without reported graft failure compared with a rate of graft failure of 4.5% in Dhédin et al.[1,3,7]. Dhédin et al. report an overall survival (OS) at 4 years of 90.15% and event free survival (EFS), defined as the proportion who survived death from any cause, GVHD, or graft failure, of 61.98%. Recently published data from CLIMB-SCD-121 using the same definitions has shown OS and EFS at 2 years both at 97.8% in SCD patients treated with exa-cel[7].

Based on exa-cel's pivotal data showing its potential to provide a one-time functional cure to patients with severe SCD, the joint EHA Specialized Working Group and EBMT Hemoglobinopathies Working Party consensus recommended gene addition/editing approaches within their regulatory indications when no HLA-matched family donor is available[8].

Finally, we fully agree with Dhédin et al.[1] and Pinto & Angelucci[2] that progress in curative treatments is advancing at a rapid pace, and that a simple comparison of the outcomes of haploidentical transplantation and gene therapy at a given point in time is not so straightforward. The choice of treatment must also take the patient's condition into account; today, some patients are not eligible for gene therapy but may benefit from a haploidentical transplant. Only thorough, long-term follow-up of both therapies will allow us to make the right decision for each patient.

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