EDITORIAL

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"*Learn and Know*" in the era of gene addition/gene editing based approaches for sickle cell disease: The EHA-EBMT consensus paper

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> "Then you better start swinnin' or you'll sink like a stone. For the times they are a-changin" RZ (Bob Dylan, Nobel prize in literature).
>
> But:
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> Adso: "Then, why do you want to know?"
>
> William of Baskervile: "Because learning does not consist only of knowing what we must or we can do, but also of knowing what we could do and perhaps should not do." (The name of the rose- Umberto Eco. 1932-2016. Italian semiologist, philosopher and writer).

Sickle cell disease (SCD) is a worldwide distributed monogenic red cell disorder with still high morbidity, limited therapeutic options, and a negative impact on patient quality of life [1–3]. Recently, gene addition/gene editing based therapeutic approaches for patients with SCD have been approved by the European Medical Agency (EMA) and the food and drug administration (FDA) and ready to be available in real world despite previous concerns on insertional oncogenesis by gene insertion [4], and limitation due to the very high product cost [5, 6]. Gene insertion is today not available in EU despite EMA approval for the lack of financial agreement with regulatory authorities. In Hemasphere, a joint action between the European Hematology Association (EHA), and the European Bone Marrow Transplantation (EBMT) societies generated a consensus paper on the identification of candidate with SCD for gene addition/ gene editing based therapy [7]. The Authors approached this topic discussing (i) the available medical treatments; (ii) the main data on hematopoietic stem cell transplantation as curative option for SCD; and (iii) the results of clinical studies on experimental and approved gene addition/ gene editing based approaches for SCD, considering also the related available follow-up. Then, the Authors focused on the risk factors for early death as well as on sickle cell related organ complications. This later might play an ambivalent role as part of indication for supportive treatment intensification to prevent further disease worsening; but also, as possible exclusion criteria, precluding the administration of the so far mandatory myeloablative conditioning [7]. The revision of the literature and the experts panel discussion allowed the generation of an algorithm for patient selection, which highlights the crucial role of close collaboration between expert centers for SCD and reference centers for hemopoietic transplantation (HCT) in patient's selection. This encourages the creation of an ad hoc communication-flow between these expert centers, which becomes even more important in the proposed medium and long-term follow-up. The panelists also identified non-eligible patients and potential future candidate in respect to sickle cell related clinical manifestations, organ damage and age. In this area of uncertainty related to the limited number of treated SCD patients and the short-term follow-up, the experts while conscious of the necessity to constructively apply the innovation "*for the times they are a-changin*" took into account the words from Willam of Baskerville in the name of the rose by U Eco: "*learning does not consist only of knowing what we must or we can do, but also of knowing what we could do and perhaps should not do*". Indeed, the experts revised and discussed the available evidence-based literature on the impact of sickle cell related organ damage, focusing on cardiovascular, liver, kidney and cerebrovascular disease as well as on erythrocyte alloimmunization and hemolytic transfusion reactions, thrombophilia or autoimmune diseases [7]. This work is truly crucial in the perspective of heterogeneity and unpredictability of acute and chronic sickle cell related clinical manifestations. These contribute to the complexity of SCD patients' selection when compared to other severe monogenic red cell disorder such as the transfusion dependent β-thalassemic patients.

In the present scenario, the careful selection of patients with SCD is also related to the technical nature and high costs involved in gene addition/editing based therapeutic approaches, considering the limited number and capacity of units capable of producing and infusing the treatment. Panelists agreed that this cellular therapy should be applied only in credited and expert centers with a specific expertise in transplantation/cellular therapy in hemoglobinopathies with a strict collaboration with an hemoglobinopathy center. This becomes critical when we consider the 2021 global burden disease (GBD) study highlighting that the number of subjects living with SCD is globally increased compared to previous GBD studies, in particular in SCD endemic areas such as the sub-Saharan countries [3]. Recently, the Lancet Hematology commission raised multiple concerns associated with SCD clinical management, in particular related to equity in the access to standard of care or emerging treatments as well as in the investment in cell therapy [8–10]. In addition, the low number of comprehensive SCD centers, the lack of integrated care for patients with SCD in low and lower-middle income countries appear to be in stark contrast with making cell therapy available in those setting [8–10]. Thus, gene addition/editing based therapeutic options make the case for the sustainability and accessibility to

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innovative treatments, which might be also shared with other hematologic disorders.

The EHA-EBMT consensus paper is a virtuous example of a collaborative project between scientific societies deeply involved in both research and clinical management of patients with SCD. Due to the intrinsic character of a consensus paper, the expert working group will be in charge for regular upgrade of the document, offering to the members of both societies and the scientific community a useful tool for making decision process in real-life.

Lucia De Franceschi[1,2] and Emanuele Angelucci[3,4]✉
[1]*Dept of Engineering for Innovative Medicine, University of Verona, Verona, Italy.* [2]*Azienda Ospedaliera Universitaria Integrata, Verona, Verona, Italy.* [3]*UO Ematologia e Terapie Cellulari, IRCCS Ospedale Policlinico San Martino, Genova, Italy.* [4]*European Group for Bone Marrow and Blood Transplantation (EBMT), Hemoglobinopathies Working Party, Genova, Italy.*
✉*email: emanuele.angelucci@hsanmartino.it*

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LDF and EA contributed to conceptualization and writing of this editorial.

COMPETING INTERESTS

EA: Data Monitoring Committee chair for Vertex and BMS, DMC member for Vifor; Consultant for Menarini-Stemline and Sanofi; Participation in advisory board for Regeneron. Received travel support from AbbVie, Sanofi and GILEAD. LDF: consultant Roche, Bristol and Agios research grant, consultant Vertex, advisory board Vifor.