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732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Differing Definitions of Vaso-Occlusion in Clinical Studies of Sickle Cell Disease Can Result in Differing Outcomes

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Background: Frequent episodes of vaso-occlusion are the hallmark of sickle cell disease (SCD), but the definition of what constitutes a vaso-occlusive episode is not consistently applied across clinical trials, creating challenges in evaluating and comparing efficacy results among different therapies. Here, we compare vaso-occlusion endpoint definitions from clinical trials for various therapies, including genetic therapies, and use clinical trial data to demonstrate the potential for outcomes differences based on differing definitions of vaso-occlusive episodes.
Methods: We reviewed completed and ongoing clinical trials and published articles using endpoints assessing the reduction or elimination of vaso-occlusive crisis/events, including trials of (i) exagamglogene autotemcel (exa-cel, CRISPR/Cas-9 based genome editing treatment), (ii) lovotibeglogene autotemcel (lovo-cel, gene addition therapy), (iii) L-glutamine, (iv) voxelotor, (v) hydroxyurea (HU) and (vi) crizanlizumab. Outcomes related to vaso-occlusion were compared across variables including care setting, care duration, treatments, and complications. Data from the CLIMB SCD-121 trial of exa-cel in patients aged 12 to 35 years with severe SCD (data cut as of 10 Feb 2023) were evaluated using different published definitions of vaso-occlusion.
Results: The most substantial differences in vaso-occlusion endpoint definitions were associated with frequency and duration of visits to medical facilities for acute pain and inclusion of specific SCD specific complications. Definitions of vaso-occlusions for acute pain related events differed across studies. The definitions of severe vaso-occlusive crises for exa-cel (severe VOC; exa-cel), sickle cell pain-related crises (SCPC; crizanlizumab and L-glutamine), and VOC (VOC; voxelotor) include events with medical facility visits of any duration (severe VOC and SCPC) or medical records of a patient being seen or contacting a physician within 1 business day of an event (VOC), whereas the definition of severe vaso-occlusive events (severe VOE; lovo-cel) requires a ≥ 24-hour hospital or emergency room (ER) observation unit visit or ≥2 visits to a day unit or ER over 72 hours. Vaso-occlusion definition for HU (painful crisis) required a facility visit of ≥4 hours duration. All endpoints include acute chest syndrome and priapism; however, the definition of severe VOE requires ≥4 visits to a medical facility for priapism to meet criterion, while others require only a single visit. The exa-cel phase 3 trial in SCD employs a broad and inclusive definition for severe VOC which counts each individual medical facility visit, regardless of frequency or duration of hospitalization. Based on this, 19 out of 20 patients (95%) met the primary endpoint of freedom from severe VOCs for at least 12 consecutive months (95% CI, 75.1%, 99.9%; P<0.0001). However, when the primary endpoint was analyzed using the severe VOE definition, all patients (20/20; 100.0%) were free from severe VOEs for at least 12 consecutive months (95% CI: 83.2%, 100.0%; P<0.0001).
Conclusions: Requirements for health care facility visits in the definitions of severe VOC (exa-cel), VOC, and SCPC were more broadly inclusive and include events that would not be counted in the definitions of severe VOE (lovo-cel) or painful crisis. Clinically, support for this observation comes from our analysis of exa-cel SCD pivotal clinical trial data using these different definitions, which showed the number of patients free from vaso-occlusive episodes changed depending on the definition of vaso-occlusion employed. These results show differences in vaso-occlusion definitions have the potential to impact assessments of treatment efficacy across different SCD therapies.

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