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Advances in science and challenges at HTA: CRISPR technologies

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Introduction and objectives

The affordability of cell and gene therapies is a key challenge, with costs incurred upfront while benefits are realized over many years. Other challenges at health technology assessment (HTA) commonly include single-arm trials and therefore lack of direct comparative efficacy data, small numbers of patients in trials, surrogate endpoints, and insufficient follow-up. Additional challenges arise for autologous cell and gene therapies (ie, where the drug product is manufactured individually for each patient) including manufacturing failure, turnaround (vein to vein) time, and specific adverse events.

Exagamglogene autotemcel (exa-cel) is the first CRISPR-based medicine to have been granted regulatory approval in Europe and the UK. The aim of this study was to compare and contrast exa-cel with previous cell and gene therapies to anticipate likely HTA challenges for CRISPR-based technologies.

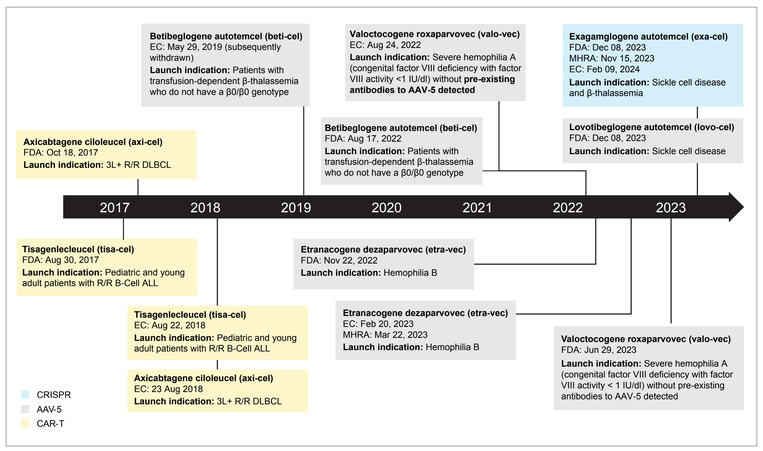
Methods

The FDA, EMA, MHRA, ICER, and NICE websites were searched for regulatory and HTA documents relating to exa-cel, which were reviewed and compared with NICE and ICER assessments for the first indication for other first-in-class cell and gene therapies for hematological conditions.

Results

Searches identified six first/early-in-class gene therapy products approved for hematological indications beyond exa-cel (Figure 1).

Figure 1: FDA, EC, and MHRA regulatory approvals for cell and gene therapies for hematological conditions



All involve gene therapy using a viral vector. Etra-vec and valo-vec are infused directly into the patient, whereas exa-cel and the other four are autologous cell therapies. All products are administered once and offer the potential for long-term benefits or cure. NICE assessments (not all were final guidance) and ICER final evidence reports (Table 1) highlighted several concerns.

- **Lack of direct comparative data:** All products received regulatory approval and were evaluated on the basis of one or more single-arm trials; therefore indirect treatment comparisons were required to establish comparative clinical benefit.
- **Uncertainty regarding long-term efficacy and safety:** Uncertainties were due to the limited numbers of patients and follow-up for all products, and the use of ORR, a surrogate outcome measure, for axi-cel and tisa-cel (Table 2).
- **Product label warnings:** Regulatory labels for all products include warnings of the risk of oncogenesis/mutagenesis/malignancies due to transgene integration, while for exa-cel a "theoretical risk of oncogenesis related to gene-editing" is noted. For cell therapies (including exa-cel), adverse events associated with conditioning treatment were also highlighted.
- **Product manufacturing/patient drop-out between enrollment and infusion:** For the cell-therapies, including exa-cel, some patients discontinued from studies between enrollment and infusion. The numbers of, and reasons for, discontinuations were not always clear.
- **Uncertainty regarding uptake of products:** Some patients withdrew consent during trials of therapies for sickle-cell disease, thalassemia, and hemophilia.

Table 1: HTA outcomes

Product	Assessment (date)	Assessment outcome
Exa-cel	NICE Draft Guidance ID4016 (March 2024)	Initial draft not recommended, final in progress
	ICER Gene Therapies for Sickle Cell Disease Final Evidence Report (Aug 2023)	May be comparable, result in incremental or substantial net benefit compared with standard of care (C++)
Lovo-cel		At least an incremental net benefit compared with standard of care and may provide a substantial net health benefit (B+)
Tisa-cel	NICE FAD TA554 (Dec 2018)	Recommended in CDF
	ICER Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers Final Evidence Report (March 2018)	At least a small net health benefit compared with current salvage chemotherapy, although the benefit may be substantial (B+)
Axi-cel	NICE FAD TA 559 (Nov 2018)	Recommended in CDF
	ICER Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers Final Evidence Report (March 2018)	At least a small net health benefit compared with current salvage chemotherapy although the benefit may be substantial (B+)
Beti-cel	NICE ACD ID968 (Feb 2021)	Not recommended (draft outcome), then discontinued
	ICER Betibeglogene Autotemcel for Beta Thalassemia (July 2022)	Superior overall to the current standard of care, but the magnitude of that overall net health benefit is less certain, ranging from incremental to substantial (B+)
Etra-vec	NICE Draft Guidance Consultation ID3812 (July 2023)	Initial draft not recommended, final in progress
	ICER Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A (Dec 2022)	Moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit compared with factor IX prophylaxis (B+)
Valo-vec		• Low certainty about the net health benefit compared with emicizumab (I) • Moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit compared with factor VIII prophylaxis (C++)

ACD, appraisal consultation document; CDF, Cancer Drugs Fund; FAD, final appraisal determination

Table 2: Data available when assessed by HTA agencies and/or regulators

Product	Patient numbers	Follow-up	Primary endpoint
Exa-cel	EPAR Dec 2023: 58 patients with SCD underwent mobilization/apheresis, 11 patients discontinued prior to infusion, 43 patients infused (4 awaiting infusion at time of data cut)	NICE: 30 people followed up for an average of 20.1 months (range: 13.6-43.6 months)	Proportion of participants who have not experienced any severe VOC for at least 12 consecutive months
	PI Dec 2023: At interim analysis 63 patients enrolled, 58 started mobilization, 6 patients were unable to receive therapy due to not achieving the minimum dose, 44 patients infused and formed the FAS	ICER: Efficacy: 17 of 35 enrolled were evaluable for primary endpoint. Safety: median follow-up 11.6 months (range: 2.0-39.1 months) PI Dec 2023: 31 patients from the FAS had adequate follow-up to allow evaluation of the primary efficacy endpoint	
Lovo-cel	PI Dec 2023: 43 patients apheresed, 7 discontinued prior to conditioning, 36 conditioned, 36 infused	ICER: 31 patients evaluable for efficacy PI Dec 2023: The median duration of follow-up (N = 36) was 38 months post-infusion (range:12-61 months)	Proportion of participants achieving complete resolution of severe VOEs 6-18 months post-infusion
Tisa-cel	EPAR June 2018: ELIANA 92 patients enrolled, 17 discontinued prior to infusion, 75 patients infused (FAS) B2205J 35 patients, 29 were infused B2101J 56 patients; enrolled vs infused not clear NICE: 236 patients in 3 trials Pooled results from patients infused in these trials n = 193	NICE: median follow-up in each study was less than 3 years	Overall remission rate
	ICER: 198 enrolled in 3 studies, 159 infused	ICER: median follow-up 8.7 months for ELIANA	
Axi-cel	EPAR June 2018: 111 patients leukapheresed 110 lots of axi-cel manufactured 101 patients infused	EPAR: median follow-up 11.3 months NICE: median follow-up 15.4 months	Overall response rate
	ICER: 111 enrolled, 101 infused	ICER: median follow-up in ZUMA-1 15.4 months	
Beti-cel	EPAR April 2019: HGB-204 (N = 18) HGB-205 (N = 4) with TDT HGB-207 (N = 23) ICER: HGB-204 (N = 18) HGB-205 (N = 4) HGB-207 (N = 23) HGB-212 (N = 18) 41 patients in the Phase 3 trials (which were the focus of the review) received beti-cel	NICE: Data from 24 people were evaluable for TI in manufacturer submission and for 54 people with 24 months follow-up at July 12, 2023 committee meeting ICER: HGB studies 2 year follow-up For the 63 patients enrolled in the long-term follow-up study, median length of follow-up of 42 months (range 23-88 months)	Proportion of participants who achieved TI for a continuous period of ≥12 months, and beginning within 12-24 months of infusion
Etra-vec	EPAR Dec 2022: HOPE-B trial 54 patients treated (67 entered lead-in phase)	NICE: 6 of 55 people (52 HOPE-B and 3 AMT-061-01) in the analysis had 24 months follow-up data; 30 months follow-up available for 3	ABR
	ICER: HOPE-B 54 patients treated AMT-061-01 3 patients	ICER: HOPE-B: 52 weeks follow-up AMT-061-01: 3 years follow-up	
Valo-vec	ICER: Phase 3 GENEr8-1: 134 patients Phase 1/2 BMN 270-201: 7 patients	ICER: GENEr8-1: 2 year follow-up BMN 270-201: 6 years follow-up	ABR

ABR, annualized bleeding rate; EPAR, European Public Assessment Report; FAS, full analysis set; PI, Package Insert (FDA); SCD, sickle-cell disease; TDT, transfusion-dependent beta-thalassemia; TI, transfusion independence; VOC, vaso-occlusive crisis; VOE, vaso-occlusive events

Conclusions

- The challenges faced by exa-cel at HTA are aligned with those previously seen in assessments of cell and gene therapies; future CRISPR-based products will likely face similar challenges.
- Long-term efficacy (durability of gene therapy) and safety are likely to continue to be a focus for regulators and HTA agencies; manufacturers should seek to enroll patients in long-term follow-up studies and expect registries to be required.
- Uncertainty regarding the trajectory of uptake in non-fatal conditions makes it difficult to get an accurate estimate of the budget impact of introducing these therapies with high unit costs. While slower uptake reduces budget impact from the upfront cost of therapy, it also delays cost offsets.

Poster presented at ISPOR US, May 5–8, 2024, Atlanta, GA, USA