



Living with Recurrent Vaso-Occlusive Crises: A Narrative Review of Gene Therapy for Sickle Cell Disease and What Curative Intent Changes for Patients and Families

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Abstract

For most of the history of sickle cell disease, treatment meant reducing the frequency of crises rather than ending them. Gene therapy offers something the field has not previously had to describe to patients: the prospect of a life without vaso-occlusive crises at all.

Objectives: *To review the published evidence on gene therapy for severe sickle cell disease: what the trials achieved, on how many patients and over what period, what the treatment requires of the person receiving it, and what remains unknown at the point of licensing.*

Material and Methods: *Narrative review of phase 1 to 3 trials, natural history studies, guideline documents and health-economic analyses indexed in PubMed and the major haematology journals. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *In the pivotal phase 3 study, 44 patients aged 12 to 35 with at least two severe vaso-occlusive crises in each of the two preceding years received exagamglogene autotemcel. Of the 30 with sufficient follow-up, 29 (97 per cent, 95% CI 83 to 100) were free of severe vaso-occlusive crises for at least 12 consecutive months, and all 30 (100 per cent, 95% CI 88 to 100) were free of hospitalisation for one. Median follow-up was 19.3 months (range 0.8 to 48.1). The safety profile was consistent with myeloablative busulfan conditioning, and no cancers occurred.*

Conclusion: *The effect size is as large as any in haematology, and the evidence base is thirty patients followed for a median of nineteen months. Both statements are true and both belong in the conversation, alongside the cost of the treatment itself: myeloablative conditioning, probable infertility, weeks in hospital, and a price that places it out of reach of most of the world's patients.*

Abbreviations: *exa-cel – Exagamglogene Autotemcel, HbF – Fetal Haemoglobin, HSCT – Haematopoietic Stem Cell Transplantation, HSPC – Haematopoietic Stem and Progenitor Cell, SCD – Sickle Cell Disease, VOC – Vaso-Occlusive Crisis, CI – Confidence Interval.*

Keywords: *Sickle Cell Disease; Gene Therapy; Vaso-Occlusive Crisis; CRISPR-Cas9; Curative Intent*

Introduction

Sickle cell disease is caused by a single nucleotide substitution and produces a lifetime of unpredictable, severe pain, progressive organ damage and shortened life expectancy [1,2], with mortality and pain frequency characterised in landmark cohorts [24,25] and survival still short even in high-income settings [26]. It is among the commonest severe monogenic disorders worldwide, and the great majority of those affected live in sub-Saharan Africa and India [3,4], where even hydroxyurea has only recently been shown feasible at scale [22].

Treatment has until recently meant modifying the frequency and severity of crises rather than preventing them. Hydroxyurea remains the mainstay and works by raising fetal haemoglobin [5,6]; more recent agents target polymerisation and adhesion with smaller effects [7,8]. Allogeneic transplantation can be curative but requires a matched donor and carries the risk of graft-versus-host disease [9,10].

Gene therapy proceeds from the same insight as hydroxyurea, that fetal haemoglobin prevents sickling, and applies it directly. Exagamglogene autotemcel edits the erythroid-specific enhancer of BCL11A in the patient's own stem cells using CRISPR-Cas9, removing the repression of fetal haemoglobin [11,12]. The target was identified through a decade of work establishing BCL11A as the developmental repressor and its erythroid enhancer as a druggable point [28,29,30], and alternative silencing and promoter-editing approaches have also reached patients [27,31]. A lentiviral approach adds a modified beta-globin gene instead [13,14]. This review examines what the trials showed and what they did not.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and general medical journals were searched for studies of gene therapy and curative approaches in sickle cell disease. Search terms combined sickle cell disease with gene therapy, gene editing, CRISPR, BCL11A, lentiviral, exagamglogene, lovotibeglogene, haematopoietic stem cell transplantation and vaso-occlusive crisis. Reference lists of guidance documents [15,16] were screened by hand for primary sources.

Eligibility: Studies were included if they reported clinical outcomes of gene therapy or transplantation in sickle cell disease, described the natural history against which those outcomes are judged, or addressed access and cost. Studies in transfusion-dependent thalassaemia are cited where they establish the platform and are identified as such.

Data extraction and handling: Design, sample size, entry criteria, follow-up duration and reported outcome were extracted as published. Sample size and follow-up are reported alongside every efficacy figure, because both are small relative to the claims the therapy invites. No pooling or re-analysis was

performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The pivotal trial: A phase 3, single-group, open-label study enrolled patients aged 12 to 35 years with sickle cell disease who had experienced at least two severe vaso-occlusive crises in each of the two years before screening. Autologous CD34+ cells were edited with CRISPR-Cas9 at the erythroid-specific enhancer of BCL11A, and patients underwent myeloablative conditioning with busulfan before infusion. A total of 44 patients received exa-cel, and neutrophils and platelets engrafted in every one [11].

The result: Of the 30 patients with sufficient follow-up for the primary analysis, 29 (97 per cent, 95% CI 83 to 100) were free of severe vaso-occlusive crises for at least 12 consecutive months, and all 30 (100 per cent, 95% CI 88 to 100) were free of inpatient hospitalisation for a severe crisis over the same period (Figure 1) [11]. Every one of these patients had entered the trial with at least two severe crises a year for two years, so the comparison against their own history is stark.

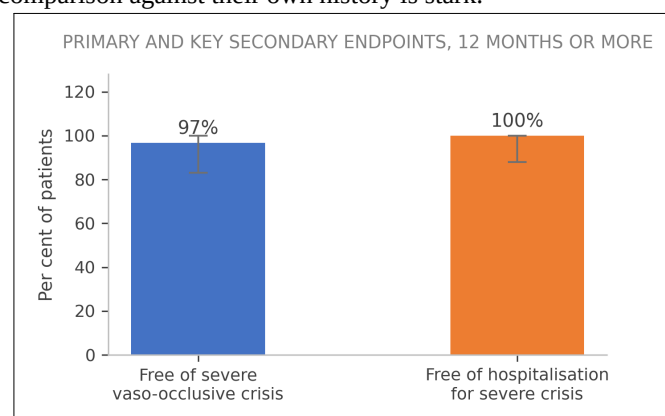


Figure 1: Primary and key secondary endpoints in the phase 3 trial, with 95% confidence intervals [11]

How many patients, for how long: The numbers behind those percentages are worth stating explicitly. Forty-four patients were infused; 30 had been followed long enough to be evaluated; 29 met the primary endpoint (Figure 2). Median follow-up across the cohort was 19.3 months, with a range of 0.8 to 48.1 months (Figure 3) [11]. For a therapy offered as a one-time and potentially permanent intervention in a disease that runs for decades, that is a short observation window, and it is the principal limitation of everything that follows.

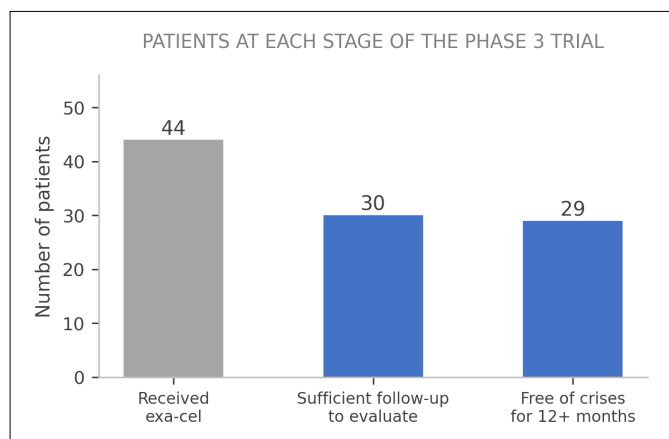


Figure 2: Patients at each stage of the phase 3 trial [11]

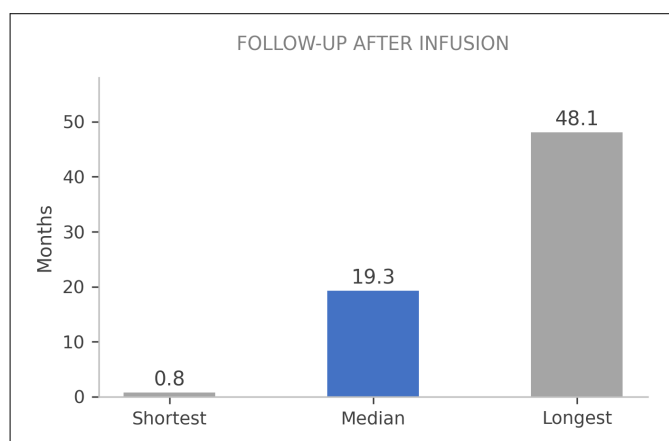


Figure 3: Follow-up after infusion across the treated cohort [11]

What small numbers can establish: A point estimate of 97 per cent from 30 patients carries a lower confidence bound of 83 per cent, and the 100 per cent hospitalisation-free figure has a lower bound of 88 per cent (Figure 4) [11]. Those lower bounds are the honest floor of what the trial demonstrates. They remain impressive, and they are not the same as the headline.

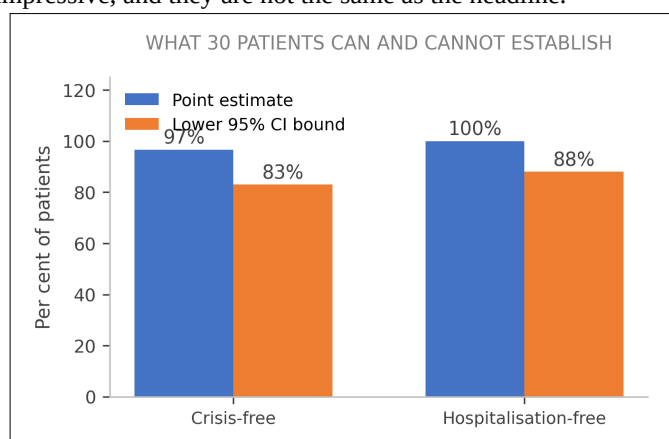


Figure 4: Point estimates against the lower bound of the 95% confidence interval in the primary efficacy population [11]

Study	Design and cohort	Principal reported finding
Frangoul et al. 2024 [11]	Phase 3, single-group, 44 infused	29/30 (97%) free of severe VOC for 12+ months; 30/30 hospitalisation-free
Frangoul et al. 2021 [12]	First-in-human CRISPR editing report	Established the BCL11A enhancer editing approach in SCD and thalassaemia
Kanter et al. 2022 [13]	Phase 1/2, lentiviral beta-globin addition	An alternative gene-addition platform in severe SCD
Charache et al. 1995 [5]	RCT of hydroxyurea	Established the comparator: fewer crises, not none
Gluckman et al. 2017 [9]	Registry, allogeneic transplantation	Curative with a matched donor; GVHD and donor availability limit it
Piel et al. 2017 [1]	Review of disease and epidemiology	Natural history and global distribution of the disease
Vichinsky et al. 2019 [7]	RCT of voxelotor	Raises haemoglobin; effect on crises limited

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

What it costs the patient: The efficacy figure describes only one side of the exchange. Receiving exa-cel means stem cell mobilisation and apheresis, myeloablative busulfan conditioning, a period of profound cytopenia, and weeks in hospital [11,17]. Busulfan carries a high probability of permanent infertility, which is a substantial matter for a population whose median age at treatment is in the twenties, and fertility preservation must be arranged beforehand [18,19]. The safety profile reported was consistent with that of myeloablative conditioning and autologous transplantation rather than with the editing itself, and no cancers occurred during the reported follow-up [11].

What it costs everyone else: The therapies were licensed at prices that place them among the most expensive medicines ever approved, and health-economic analyses have reached varying conclusions depending on the assumptions made about durability [20,21]. The distributional problem is sharper than the affordability one. The great majority of people with sickle cell disease live in countries without the transplantation infrastructure that gene therapy presupposes [3,4,22]. A treatment requiring apheresis, cell manufacture, myeloablation and prolonged inpatient care is not, on current delivery models, available to them.

Consideration	What is established	What is not
Crisis prevention	29 of 30 free of crises for 12+ months	Whether this persists beyond a few years [11]
Hospitalisation	30 of 30 free of admission for crisis	Effect on other complications of the disease [11]
Organ damage	Not an endpoint in the trial	Whether existing damage stabilises or reverses [1,11]
Safety	Consistent with busulfan conditioning; no cancers	Long-term malignancy risk after gene editing [11,18]
Fertility	Myeloablation carries high infertility risk	Discussed as a certainty rather than a side effect [18,19]
Access	Licensed in high-income settings	Any delivery model for where most patients live [3,22]

Table 2: What the trial evidence establishes about gene therapy, and what it leaves open

Discussion

It is difficult to overstate the clinical significance of a patient with two or more severe crises a year having none for a year. Anyone who has looked after this population knows what the alternative looks like, and the trial result is not a marginal improvement in a surrogate marker. It is the outcome the disease is defined by, abolished in almost everyone treated [11].

The reasons for restraint are about the evidence rather than the effect. Thirty patients were evaluable, follow-up ran to a median of 19.3 months, and there was no control group [11]. A single-group design is defensible here, since each patient's own crisis history provides a strong comparator and randomising against placebo would be difficult to justify. But it means the durability question is entirely open. Fetal haemoglobin induction is being asked to persist for decades in a self-renewing stem cell population, and nineteen months does not test that.

A second gap concerns what was not measured. The endpoints were crises and hospitalisation. Sickel cell disease also causes stroke, pulmonary hypertension, renal failure, avascular necrosis and cognitive impairment, largely through chronic haemolysis and vaso-occlusion that occur between crises [1,2,23]. Whether abolishing crises halts that trajectory, and whether damage already present improves, is not addressed by these trials and is arguably the more important question for a patient in their twenties. Patient-reported surveys describe a burden extending well beyond the crisis itself [35].

The third issue is the one least discussed in the trial reports. A therapy that requires myeloablation is not a gentler alternative to transplantation; it is transplantation without the donor. The conditioning is the same, the hospital stay is the same, and the near-certain infertility is the same [17,18,19]. What is avoided is graft-versus-host disease and the need for a matched donor, which is a genuine and substantial gain. But describing this to a patient as a cure without also describing busulfan would be a serious failure of consent.

Study limitations

The limitations belong to the underlying literature. The pivotal trial was single-group and open-label, with 30 patients evaluable and a median follow-up of 19.3 months [11]. Entry was restricted to those aged 12 to 35 with frequent severe crises and fit enough for myeloablation, so the results do not extend to older patients, those with established organ damage or those with milder phenotypes. Endpoints were crises and hospitalisation, not organ function, mortality or quality of life [11]. The two gene therapy platform was established in transfusion-dependent thalassaemia first [33,34]. The two platforms have not been compared with each other, nor either against allogeneic transplantation [11,13]; development and regulatory considerations have been set out separately [32]. Long-term risks of gene editing, including malignancy, cannot be excluded on this duration of follow-up [18]. Cost-effectiveness estimates depend on durability assumptions that the data do not yet support [20,21]. And essentially all of the evidence comes from high-income settings [3,22].

Conclusion

Gene therapy has done something no previous treatment for sickle cell disease has managed: it stopped the crises. In 29 of 30 evaluable patients, a disease defined by recurrent, unpredictable, severe pain produced none for at least a year. That deserves to be described plainly and without hedging. It also deserves to be described completely, which means saying that the evidence is thirty patients over a median of nineteen months, that the treatment is myeloablative conditioning with the infertility that implies, that nothing is yet known about organ damage or durability, and that the delivery model puts it beyond the reach of most people who have the disease. The conversation with a patient sitting in clinic has to contain both halves.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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