hematologic normalization and renal recovery, especially when initiated early. Ravulizumab, a long-acting C5 inhibitor requiring infusions every 8 weeks, offers comparable efficacy with improved quality of life. Real-world studies confirm their sustained safety and effectiveness, though concerns regarding meningococcal infections necessitate vaccination and antibiotic prophylaxis. The duration of therapy remains debated; relapse occurs in 20–30% after discontinuation, particularly in carriers of CFH and CFI mutations. Emerging biomarkers and genetic stratification may enable more personalized discontinuation strategies. **Challenges and Future Perspectives:** Despite therapeutic advances, significant challenges remain. Complement inhibitors impose a lifelong economic burden, raising questions of cost-effectiveness and accessibility. Health-economic analyses highlight the need for balanced strategies between clinical benefit and financial sustainability. Furthermore, gaps persist in standardized diagnostic criteria, access to genetic testing, and long-term outcome data for ravulizumab. Ongoing research focuses on refining biomarkers for risk stratification, identifying novel complement targets, and developing more affordable therapies. Special considerations arise in pregnancy-associated aHUS, post-transplant recurrence, and pediatric populations, where individualized management is critical. In conclusion, aHUS exemplifies a paradigm shift in the treatment of rare complement-mediated diseases. Early recognition, integration of genomic data, and targeted complement inhibition have transformed its prognosis. Future research must focus on optimizing therapeutic duration, expanding access to novel agents, and achieving a cost-effective, precision medicine approach for this devastating disorder.

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**Abstract 035**

## CURATIVE TREATMENT APPROACHES IN THALASSEMIA

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Supportive therapies prolong survival in transfusion-dependent $\beta$-thalassemia (TDT), however they do not eradicate the disease. Advances in hematopoietic stem cell transplantation (HSCT), gene therapy, and gene editing technologies have transformed the therapeutic landscape and brought curative options into clinical practice. Allogeneic HSCT remains the most established curative treatment for thalassemia. In HLA-matched sibling transplantation, event-free and thalassemia-free survival exceed 80–90% in children transplanted at an early stage. Younger patients without advanced iron overload consistently achieve superior outcomes, highlighting the importance of early referral. Alternative donor strategies are being increasingly explored. Haploidentical HSCT using post-transplant cyclophosphamide (PTCy)-based regimens has improved survival rates to 60–70%, though graft failure and graft-versus-host disease (GVHD) remain major limitations. Umbilical cord blood transplantation, although feasible, is hampered by limited cell dose and delayed engraftment. Novel approaches such as $\alpha/\beta$ T-cell depletion or infusion of regulatory T-cells are under investigation to mitigate GVHD and reduce graft loss. Beyond allogeneic transplantation, lentiviral gene therapy represents a major breakthrough. Autologous $CD34^+$ hematopoietic stem cells can be transduced with a lentiviral vector encoding a functional $\beta$A-T87Q-globin gene. In early phase trials such as HGB-204 and HGB-205, 75–80% of patients achieved transfusion independence for ≥12 months. Phase III studies (Northstar-2 and Northstar-3) confirmed long-term transfusion independence in over 80% of non-$\beta0/\beta0$ genotypes and around 70% of $\beta0/\beta0$ patients. Toxicities are mainly conditioning-related, with busulfan causing cytopenias, hepatic veno-occlusive disease, and infertility. Importantly, no insertional leukemogenesis has been reported. Betibeglogene autotemcel (Zynteglo®) received EMA approval in 2019 and FDA approval in 2022, yet its high cost is a significant barrier to widespread adoption. Long-term safety and durability of benefit are being assessed in the ongoing LTF-303 follow-up study. CRISPR-Cas9 gene editing has introduced a paradigm shift in curative approaches. Exagamglogene autotemcel (Exa-cel) works by inactivating the BCL11A erythroid enhancer, thereby reactivating fetal hemoglobin (HbF) and providing a mutation-independent therapeutic effect. Regulatory agencies have rapidly recognized its impact: the MHRA in the UK approved Exa-cel in November 2023 for both TDT and SCD, while the FDA granted approval in December 2023 (SCD) and January 2024 (TDT). EMA approval is pending, with PRIME designation already granted. Safety data so far suggest that adverse events are primarily busulfan-related, with no evidence of genotoxicity or malignant clonal expansion. Additional curative strategies are under early investigation. Other gene editing platforms, such as TALENs and zinc-finger nucleases, may allow more controlled cleavage activity, though their clinical application remains experimental. Pharmacologic HbF induction is another promising avenue. Hydroxyurea has limited efficacy in TDT but modest benefit in HbE/$\beta$-thalassemia. Novel small molecules such as mitapivat, a pyruvate kinase activator, have shown hemoglobin improvement in non-transfusion-dependent patients, and Phase III trials are ongoing. LSD1 inhibitors and pomalidomide derivatives are in preclinical or early clinical development as pharmacologic HbF inducers. From a clinical perspective, HSCT remains the gold standard in eligible patients with a matched donor, while refined haploidentical protocols are expanding donor availability. Gene therapy offers a curative option for patients lacking suitable donors, though conditioning-related toxicity, accessibility, and cost limit its use. CRISPR-based genome editing has shown transformative efficacy, but long-term safety monitoring is essential before universal adoption. In conclusion, curative treatment for thalassemia has expanded far beyond traditional transplantation. Lentiviral gene therapy and CRISPR-based editing represent a paradigm shift, offering functional cures in the majority of treated patients.

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