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Advances in ß-Thalassemia: From Molecular Biology to Clinical Practice

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Abstract

Beta-thalassemia (ß-thalassemia) is an autosomal recessive disorder of haemoglobin inheritance resulting due to mutations of HBB gene present on chromosome 11 that lead to quantitative deficiency of ß-globin chains. The defect results in the accumulation of unpaired α-globin chains, inducing high rates of apoptosis in erythroid precursors, ineffective erythropoiesis, severe anaemia and progressive systemic iron overload. The conventional clinical approach is lifelong blood transfusion with regular iron chelation therapy but patients remain at risk of secondary organ toxicity. This review delineates the rapid paradigm shift in management of ß-thalassemia from conventional, supportive strategies toward personalised precision medicine. It discusses critical modern diagnostic methodologies, such as high- performance liquid chromatography (HPLC) and multiplex ligation-dependent probe amplification (MLPA), alongside pioneering therapeutic interventions. This paper reviews the clinical efficacy, regulatory milestones and mechanisms of action of the recently FDA-approved autologous hematopoietic stem cell gene therapies and CRISPR/Cas9-based gene-editing systems. It also discusses new targeted drug therapies and novel hepcidin-ferroportin axis modulators. It highlights important implementation challenges, including high costs of treatment, disparities in access across the world, and the integration of multi-omics data, and emphasizes the pathways needed to translate these advanced genomic innovations into accessible curative clinical standards on a global scale.

Keywords: ß-thalassemia, iron chelation therapy, precision medicine, targeted drug therapies.

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1. Introduction

Blood disorders characterized by quantitative deficiency of globin chains present in the hemoglobin molecule are referred as thalassemia.[1] ß-thalassemia, an inherited disorder, results when an inadequate amount of ß-globin chains leads to accumulation of α-globin chains, resulting α-ß globin chain imbalance resulting inability to produce

hemoglobin essential to carry oxygen in red blood cells.[2,3] ß-thalassemia patients are known to experience severe anaemia due to low oxygen levels and must require blood transfusion throughout life since early childhood.

According to global burden of 2021, ß-thalassemia accounts approximately 1.31 million prevalent cases worldwide, with annual birth of nearly 40,000-60,000 infants with severe transfusion-dependent thalassemia and additionally, 56,000 infants with non-transfusion dependent thalassemia.[4] In India, an estimated 43-58 million people are known to carry the defective gene (which account 25% of the global burden of 2021), with national prevalence of 3.74%. Furthermore, active ß-thalassemia patients in India accounts over 100,000-150,000.[5,6] The states of western and northern region of India are observed with highest burden of ß-thalassemia cases due to several factors such as, historical migration patterns, non-random mating, etc.[7]

Thalassemia is categorized into two types based upon the number of defective genes present in the alpha and beta globin chains, i.e. Alpha thalassemia and Beta thalassemia, respectively.[2] The two α-globin genes HBA1 and HBA2 are found as α-globin cluster on chromosome 16 and HBB gene for γ, δ and ß-globin chains as ß-globin cluster found on chromosome 11.[6] The mutations of genes are usually inherited in an autosomal recessive manner.[8] ß-thalassemia is one of the most prevalent genetic disorders ranging from asymptomatic conditions to severe transfusion-dependent cases. When left untreated, ß-thalassemia becomes fatal.[9,10,11]

Depending upon genetic severity and transfusion requirements, ß-thalassemia is classified into three forms: ß-thalassemia minor (one altered gene), ß-thalassemia intermedia (two altered gene) and ß-thalassemia major (two highly defective genes). ß-thalassemia minor represents the asymptomatic carrier state requiring no medical intervention, ß-thalassemia intermedia presents with moderate severity where patients are usually non-transfusion dependent but requires occasional therapies. ß-thalassemia major is the most severe form which is fatal and requires frequent blood transfusion throughout life.[1,11]

Diagnosis at preliminary level, involves biochemical and chemical assessment, which includes complete blood count (CBC) analysis, Hemoglobin levels, Measurement of serum ferritin and serum transferrin, liver function, cardiac function, bone health markers, etc.[10] Frequent blood transfusion observes some adverse effects to the body, such as heart failure, growth retardation, liver cell dysfunction, diabetes mellitus despite expanded use of iron chelating drugs.[12,13]

Beyond conventional laboratory work, *in silico* work gaining attention in most of the research areas. Computational modelling of protein involved in study helps revealing new molecular targets of therapy. Further, docking and simulation techniques works for cost-effectiveness and time saving.

This review addresses how treatment of ß-thalassemia is shifting from traditional blood transfusions to personalised precision medicine. Paper highlights newly approved gene therapies and targeted drugs which can help reduce lifelong blood transfusion need of patient.

2. Molecular Biology of ß-Thalassemia

2.1 Hereditary Transmission

ß-thalassemia disorders are inherited in an autosomal recessive manner where parents are heterozygotes and carry a single copy of a ß-globin gene mutation which can cause ß-thalassemia when transferred to their children. The child gets 25% chance of been affected, 50% chance for being an asymptomatic carrier and 25% chance of being unaffected with disease but carrying the disease trait.[2]

2.2 Molecular Pathophysiology

The mutation in the HBB gene located on the chromosome 11p15.4, encoding the ß-globin chain of adult haemoglobin results in ß-thalassemia.[10] The mutations results in single nucleotide substitution, small deletions or insertions withing the ß-globin gene or its immediate flanking sequence, or in rare cases, gross deletions leading to reduced production of ß-globin chains and HbA. Several mutations have been identified which suggested categorization into $ß^0$, when complete absence of ß-globin production and $ß^+$ when ß-globin production is reduced but not absent.[14] The HBB mutation type influences the clinical severity of ß-thalassemia, i.e., two severe $ß^0$ mutations ($ß^0/ß^0$) develop transfusion-dependent thalassemia major, while compound heterozygotes ($ß^0/ß^+$) or homozygous mild $ß^+$ mutations results into wide range of phenotypic expressions, from transfusion-dependent major to non-transfusion dependent intermediate forms, depending upon residual ß-globin production.[10,15] Individual with ß-thalassemia major are usually found as asymptomatic at birth due to the presence of HbF, but becomes symptomatic by six months of age.[16] (Figure.1.)

The fundamental anomaly is the disproportion between the α-and ß-globin chains. In erythroid precursors, excess

unpaired α-globin chains get accumulated creating toxic inclusion bodies which damages cell membranes, produces reactive oxygen species (ROS), induces oxidative stress, and initiate apoptosis.[14] Ineffective erythropoiesis occurs, when there is high rate of apoptosis, up to 70-80% of erythroid precursors.[10] Red blood cells entering the circulation still consists of α-chain inclusions. This inclusion makes red blood cells rigid leading to extravascular haemolysis, mostly seen in spleen.[17]

2.3 Genetic Modifiers

The ß-globin (HBB) gene, located on the short arm of chromosome 11 and belongs to cluster of ß-globin gene, which contains the δ-globin gene, the embryonic ε-gene, the fetal A-γ and G- γ genes, and a pseudo-gene (ψB1) arranged in manner of their developmental expression. HBB gene is approximately 1.6 kb long containing three exons and 5' and 3' untranslated regions, and is regulated by a promoter with TATA, CAAT and CACCC elements. The expression is mainly regulated by the upstream locus control region (LCR) consisting of four erythroid-specific DNase I hypersensitive sites (HS1-HS4) that attract transcription factors, such as GATA-1, NF-E2, KLF1 and FOG-1. Among these, KLF-1 is particularly important for ß-globin transcription by binding to the CACCC box.[3]

ß-thalassemia is known to be existing with extensive molecular heterogeneity, with >200 pathogenic variants identified in HBB. Most are either point mutations or small insertions/deletions with large gene deletions being relatively uncommon. Mutation resulting complete loss of ß-globin production give rise to $ß^0$-thalassemia and includes nonsense, frameshift, initiation codon, deletion and splicing defects. In contrast, $ß^+$-thalassemia results from reduction in ß-globin synthesis due to abnormalities in promoter regions, UTRs, polyadenylation signals or RNA splicing. Variants are categorized on the basis of their functional effect into severe or mild category.[18] [3]

Few rare defects observed in HBB gene involve other regulatory genes, including TFIIH and GATA-1. Despite the existence of many mutations, in each ethnic group, most-disease causing alleles are caused by a few population-specific variants.[19,20]

The ß-thalassemia phenotype is further modulated by few other genetic modifiers present outside the HBB cluster. For example, UGT1A1 variants associated with Gilbert syndrome may increase unconjugated hyperbilirubinemia and gallstone formation. The GSTM1-null genotype has been linked to increased myocardial iron deposition. Also, variants in HFE and genes involved in bone metabolism may affect disease complications.[21–24]

3. Iron Metabolic Pathway

Iron metabolism is a highly regulated physiological process and mainly controlled by several types of mechanisms targeting intestinal absorption. Approximately 60-70% of total body iron is incorporated into haemoglobin, around 20% is stored as ferritin, while the remaining iron is distributed among myoglobin, transferrin, and various iron-containing enzymes.[25] Brush border enzyme duodenal cytochrome B (Dcytb) located on the apical surface of enterocytes reduces dietary non-heme iron from ferric (Fe^{3+}) to ferrous (Fe^{2+}).[26] Ferrous iron is subsequently transported into enterocytes through divalent metal transporter 1 (DMT1). Iron is then exported across the basolateral membrane by ferroportin, the only known cellular iron exporter, and is oxidized before binding to transferrin for systemic transport to peripheral tissues.[27] In addition, plasma also contains non-transferrin-bound iron (NTBI), which becomes increasingly abundant under conditions of transferrin saturation. NTBI is readily taken up by hepatocytes and other parenchymal cells, contributing significantly towards tissue iron overload disorder in ß-thalassemia.[28]

Systemic iron homeostasis is primarily regulated by the hepcidin-ferroportin (HAMP-FPN) axis, principal mechanism controlling intestinal iron absorption, iron recycling, and iron storage.[29] Hepcidin, a 25-amino acid antimicrobial peptide encoded by the HAMP gene on chromosome 19q13, is synthesized predominantly by the liver and acts as the master regulator of iron metabolism. It binds to ferroportin (FPN), the only known cellular iron exporter encoded by SLC40A1 gene on chromosome 2q32, inducing its internalization and degradation, resulting reduced dietary iron absorption and iron release from macrophages and hepatocytes. Consequently, hepcidin-ferroportin interaction regulates iron homeostasis by (i) inhibiting duodenal iron, (ii) suppressing iron recycling from macrophages, and (iii) limiting iron mobilization from hepatic stores, thus maintaining plasma iron homeostasis.[30–32]

In ß-thalassemia, ineffective erythropoiesis suppresses hepatic hepcidin production, resulting in increased ferroportin activity, excessive intestinal iron absorption, and progressive systemic iron overload.[10] This process is further exacerbated by erythroferrone (ERFE), an erythroid-derived hormone that inhibits HAMP

transcription to enhance iron availability for erythropoiesis.[33]

Matriptase-2, encoded by the TMPRSS6 gene, is a type II transmembrane serine protease that plays crucial role in regulation of iron homeostasis. Under iron-deficient conditions, matriptase-2 cleaves membrane-bound hemojuvelin (HJV), thereby inhibiting the bone-morphogenetic protein-SMAD (BMP-SMAD) signalling pathway, a major positive regulator of HAMP transcription.[34] This suppression result in reduced hepcidin production, allowing increased ferroportin-mediated iron absorption and release into the circulation.[35,36] Conversely, loss-of-function mutations in TMPRSS6 impair HJV cleavage, resulting in inappropriately high hepcidin levels and causing iron-refractory iron deficiency anaemia (IRIDA).[37,38]

4. Clinical Manifestations Related to ß-Thalassemia

Iron overload is the major and progressive complication seen in ß-thalassemia patients with frequent blood transfusions and increased intestinal absorption due to supressed levels of hepcidin.[10,39] Excess iron circulates in the form of non-transferrin bound iron (NTBI) and labile plasma iron causing oxidative stress and cellular damage because of formation of reactive oxygen species.[14] Heart is the most affected organ due to iron deposition resulting cardiomyopathy, arrythmias, and congestive heart failure.[10] Liver, the primary storage site of iron is highly susceptible to develop fibrosis, cirrhosis and hepatocellular carcinoma.[39] Deposition of iron in endocrine organs affects the metabolic and hormonal activity of the body, by developing disorders like diabetes mellitus, hypogonadism, hypothyroidism, and growth retardation.[40] Osteoporosis and reduced bone mineral density are observed as skeletal complications. Furthermore, increasing susceptibility to infections linked to pulmonary hypertension is also seen in patients due to immune dysfunction.[10] The complications observed suggests systemic nature of iron toxicity, highlighting the need of regular monitoring and proper disease management.

5. Screening & Diagnosis

5.1 Laboratory investigations

The initial screening of the disorder is commonly based on red blood cell indices, which includes reduced mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), indicating the microcytic hypochromic anaemia.[41] Thalassemia major is defined by low level Hb level (<7g/dl), mean corpuscular volume (MCV) >50<70 fl and mean corpuscular Hb (MCH) >12<20 pg. In thalassemia intermedia, Hb level is between 7 to 10 g/dl, MCV between 50 to 80 fl and MCH between 16 to 24 pg. For thalassemia minor, MCV, MCH are decreased HbA_2 level is increased.[2] Osmotic fragility, and the dichlorophenolindophenol (DCIP) tests are used to suspect hemoglobinopathies, especially HbE-related disorders.[42] High-performance liquid chromatography (HPLC) confirms the diagnosis by quantifying Hb fractions including HbA_2 and HbF levels. Elevated level of HbA_2 with mild increase in HbF confirms the ß-thalassemia trait, while normal or low HbA_2 levels confirms α-thalassemia or iron deficiency anaemia. Significantly elevated levels of HbF may indicate δß-thalassemia or hereditary persistence of fetal hemoglobin. HPLC can also be used to identify abnormal hemoglobin variants, such as HbE and HbS.[43–45]

5.2 Molecular diagnosis

Mutations in the HBB gene are routinely detected using variety of PCR-based molecular diagnostic techniques. Reverse dot blot (RDB) analysis and allele-specific PCR (AS-PCR) are most commonly employed in clinical laboratories, which utilizes mutation-specific probes or primers to identify the most prevalent HBB variants within specific populations.[46] Real-time PCR and micro-based assays have further enhanced diagnostic efficiency.[47] In cases, where targeted mutation screening fails to identify a pathogenic variant, mutation scanning methods or comprehensive gene sequencing are recommended, which offers 99% diagnostic sensitivity.[48] Furthermore, multiplex ligation-dependent probe amplification (MLPA) detects large deletions, duplications, or genomic rearrangements that may not be identified with the conventional sequencing approaches. [49]

5.3 Iron overload assessment

The standard method to evaluate the iron storage is the measurement of serum ferritin.[44,50] In addition, non-transferrin bound iron (NTBI), also referred as serum free iron, can be predicted when serum transferrin saturation exceeds 70-80%, i.e., the condition where excess iron is taken up by cells and stored as ferritin.[28]

Serum ferritin demonstrates a strong correlation with severe hepatic iron concentration, making it a useful screening tool before MRI-based evaluation.[50] However, because ferritin levels may be influenced by inflammation, infection, and liver disease, they should be interpreted alongside other clinical and laboratory findings. T2 and

T2* parameters are validated to quantify iron concentration in liver. T2* magnetic resonance imaging (T2*MRI) is the gold standard, reproducible, non-invasive technique for quantifying iron deposition in the liver, heart, and pancreas and used extensively for monitoring iron overload in transfusion-dependent thalassemia patients.[41,51]

6 Current Clinical Management

6.1 Blood transfusion

Blood transfusion to ß-thalassemia patients helps overcoming the irregular erythropoiesis by providing new erythrocytes. The administration is required every 2-3 weeks to maintain the requisite amount of Hb levels throughout life.[1] For NTDT patients, administration is needed when significant decrease in Hb levels is seen, such as, infection, stress or pregnancy.[10] In contrast, several side effects are also observed developing in TDT patients, which is treated with other therapies. Several follow up studies concluded that transfusion and iron chelation therapy are correlated and helps improving the survival of patients.[13] (Figure 1)

6.2 Iron chelation

Development of transfusional iron overload is considered the most common secondary complication in TDT patients with ß-thalassemia. Its prevention depends upon administration of appropriate chelation therapy. Most widely used iron chelators in clinical practice are Desferrioxamine (DFO), Deferiprone (DPO), and Deferasirox.[12](Figure 1)

Table 1. Characteristics of Iron-chelating drugs.

Characteristics	Iron Chelating Drugs			References
	Desferrioxamine	Deferiprone	Deferasirox	
Structure	Hexadentate	Bidentate	Tridentate	[52,53]
Dose	25-50mg/kg/day	75-100mg/kg/day	20-40mg/kg/day	[52]
Administration	Subcutaneous or intravenous injections 8-10hr/day, 5-7days/wk	Oral. Thrice a day	Oral, once a day	[54]
Mechanism of Action	Chelates NTBI, ft-bound iron; promotes ferritinophagy	Chelates labile iron in cytosol	Chelates labile iron in cytosol; increases hepcidin levels	[52,54,55]
Route of Excretion	Bilinary and urinary	Urinary	Faecal	[53]
Adverse effects	Hearing disorders, growth retardation, lung/renal toxicity, bone abnormalities, visual disorders.	Severe agranulocytosis, neutropenia, gastrointestinal problems, arthritis.	Rash, renal disorders, gastrointestinal problems	[53]

6.3 Bone Marrow Transplant

The curative approach for ß-thalassemia major is bone marrow transplantation at childhood age. Hematopoietic stem cell transplantation (HSCT) helps generally in low-risk individuals with no hepatomegaly, no portal fibrosis on liver biopsy, and regular chelation therapy.[16] Children identified before the development of viral hepatitis or

severe iron overload who receive HLA-identical related donor stem-cell transplants have very high likelihood of remission, with mortality rate of less than 10% and minimal morbidity other than impaired fertility. The unavailability of donor i.e. HLA-matched individual for young patients is the major issue.[56] The condition when the HLA-matched donor is found, allogenic HSCT is performed and when unavailability of donor, gene therapy and other approaches are focused upon.(Figure.1.)

6.4 Splenectomy

Before performing splenectomy, the observation of increased risk of venous thrombosis and pulmonary hypertension, along with overwhelming infections after splenectomy should be taken into consideration. The procedure should be avoided in small children because of a much greater risk of fulminant post splenectomy sepsis, primarily caused from encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis). The prevention includes immunization against bacteria and antibiotic prophylaxis as well as early antibiotic treatment. Main indications in thalassemia major patients for splenectomy includes increased blood requirement (>200-220 ml/kg/year) which prevents its control by iron chelation therapy, hypersplenism with cytopenias, and symptomatic splenomegaly with risk of rupture.[3]

7 Emerging Molecular Therapies

7.1 Gene therapy

Gene therapy for ß-thalassemia involves the ex-vivo transfer of a functional ß-globin gene (HBB) gene into autologous hematopoietic stem and progenitor cells (HSPCs) using a lentiviral vector, followed by reinfusion of the genetically modified cells into the patient. In the phase III HGB-212 clinical trial, betibeglogene autotemcel (beti-cel; Zynteglo) resulted in transfusion independence in 16 of 18 patients (89%) with severe transfusion-dependent ß-thalassemia (TDT). Zynteglo received approval from the U.S. Food and Drug Administration (FDA) in August 2022 for the treatment of adult and paediatric patients with transfusion-dependent ß-thalassemia.[57]

7.2 Gene editing

Exagamglogene autotemcel (exa-cel; Casgevy) known as a landmark advancement in CRISPR/Cas9-based gene editing for ß-thalassemia. Rather than correcting the HBB mutation directly, exa-cel reactivates fetal hemoglobin (HbF) expression by disrupting the erythroid -specific enhancer of BCL11A, a key repressor of y-globin production in adults.[58–60] Reactivation of HbF compensates for deficient ß-globin synthesis, thereby reducing or eliminating transfusion requirements in patients with transfusion-dependent ß-thalassemia (TDT).[61] Exa-cel received FDA approval in January 2024. In clinical studies, 39 of 42 patients (93%) achieved transfusion independence following a single treatment, while long-term follow-up demonstrated sustained clinical efficacy and significant improvements in quality of life.

7.3 HbF induction

Hydroxyurea is the most widely used fetal haemoglobin (HbF) inducer, primarily recommended for non-transfusion dependent thalassemia (NTDT). Increasing γ-globin synthesis, improves the α/ß-globin chain imbalance, reduces ineffective erythropoiesis, and raises haemoglobin levels. A meta-analysis demonstrated good response rates of approximately 65% in reducing transfusion requirements in TDT and 53% in increasing levels of haemoglobin in NTDT, with neutropenia and leucopenia being the most common adverse effects.[62] Current TIF 2025 guidelines do not recommend hydroxyurea as first-line therapy for TDT because of its variable efficacy, although selected patients, particularly those with favourable genetic modifiers (e.g., Xmnl polymorphism), may benefit. Recent studies suggest that combining hydroxyurea with thalidomide or recombinant human erythropoietin (rHuEPO) further improves haemoglobin levels and reduces transfusion requirements with acceptable safety.[63]

7.4 Ineffective erythropoiesis

Activin receptor-II ligand traps improve ineffective erythropoiesis by binding members of the TGF-ß superfamily, resulting inhibition of SMAD2/3 signalling and promoting late-stage erythroid maturation.

Sotatercept (ACE-011), an ActRIIA fusion protein, demonstrated dose-dependent increases in haemoglobin and reductions in transfusion burden in phase II studies, with a favourable safety profile. However, its development for treatment in ß-thalassemia discontinued in favour of more effective luspatercept.[64–69]

Luspatercept (ACE-536), an ActRIIB fusion protein, selectively binds TGF-ß ligands, including GDF11 and GDF8, to enhance erythroid maturation. Clinical trials demonstrated significant reductions in transfusion burden, increased haemoglobin levels, and lower serum ferritin, leading to its FDA approval in 2019 for transfusion-dependent ß-thalassemia. Related studies undergoing to

evaluate its efficacy in non-transfusion dependent ß-thalassemia and in combination therapies.[70–77]

7.5 Iron regulation therapies

7.5.1 Minihepcidins

Minihepcidins are synthetic hepcidin mimetics that restore iron homeostasis by promoting degradation of ferroportin, thereby reducing intestinal iron absorption and iron release from macrophages. In Hbbth$^{3/+}$ mouse models, they improved anaemia, ineffective erythropoiesis, splenomegaly, and tissue iron overload, with enhanced efficacy when combined with deferiprone. However, phase II trials of LJPC-401 and PTG-300 were discontinued because of lack of efficacy and related risks. Thus, minihepcidins remain unexplored for ß-thalassemia.[78–80]

7.5.2 TMPRSS6 inhibitors

Inhibition of TMPRSS6 helps in negative regulation of BMP-SMAD-hepcidin pathway. Increased hepcidin reduces intestinal iron absorption and systemic iron overload, thereby improving iron homeostasis and ineffective erythropoiesis. As per preclinical studies in mouse model, Hbbth$^{3/+}$ mice demonstrated improvement in anaemia, splenomegaly, and iron overload following TMPRSS6 suppression.[81] Other therapies under development, such as REGN7999, a fully human monoclonal antibody has shown preclinical efficacy by reducing liver iron, splenomegaly, oxidative stress, and ineffective erythropoiesis while improving RBC lifespan. Phase II FERVENT-1 trial is evaluating its efficacy in NTDT ß-thalassemia. DISC-3405, another anti-TMPRSS6 monoclonal antibody, similarly increases endogenous hepcidin and lowers serum iron, showing a favourable safety profile in phase I studies.[82,83]

7.5.3 Ferroportin inhibitor

Pharmacological inhibition of ferroportin mimics hepcidin activity, reducing plasma iron availability, limiting intestinal iron absorption, and promoting effective erythropoiesis while preventing iron overload. Vamifeport (VIT-2763), an oral ferroportin inhibitor has shown encouraging preclinical results, including improved anaemia, reduced α-globin aggregation, oxidative stress, hepatic iron overload, and ineffective erythropoiesis in ß-thalassemia mouse models. Phase II clinical trials are undergoing evaluating its safety and efficacy in patients with non-transfusion dependent ß-thalassemia (NTDT). VIT-2763 directly targets the hepcidin-ferroportin axis and possess the potential to improve anaemia and reduce iron overload.[84–89]

7.5.4 Pyruvate kinase Activator- Mitapivat

Mitapivat (AG-348) is an oral pyruvate kinase activator approved by FDA in December 2025 under the name of AQVESME for treatment of anaemia in adults diagnosed with α- or ß-thalassemia. The phase III ENERGIZE trial, significantly increased haemoglobin levels (≥1.0g/dL from baseline) in patients with non-transfusion dependent thalassemia. In the ENERGIZE-T trial, transfusion-dependent thalassemia patients shown significant reduction in transfusion requirements, with some attaining transfusion independence. It is the first therapy approved for both TDT and NTDT patients, representing major advance by improving anaemia, reducing transfusion burden, and alleviating fatigue.[90]

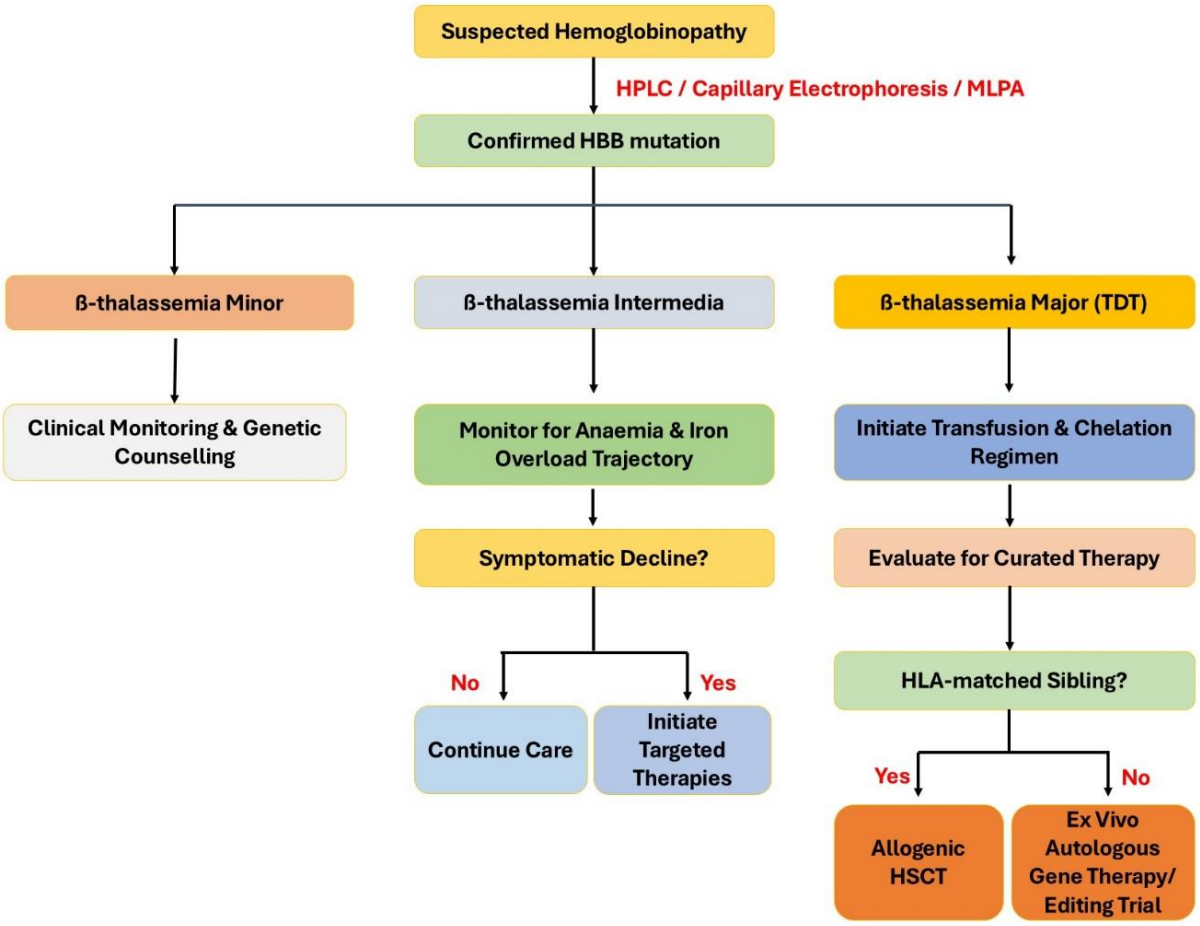


Figure 1. Clinical Management of ß-thalassemia

8. Future Directions

The integration of precision medicine with the new genomic and computational technologies will be the basis of future advances in the management of ß-thalassemia. Multi-omics approaches that integrate genomics, transcriptomics, proteomics, metabolomics and epigenomics will give a comprehensive view of disease heterogeneity and aid in the identification of new biomarkers and therapeutic targets. Single cell sequencing will likely be able to identify cellular and molecular heterogeneity in the hematopoietic niche, and thus provide deeper insights into ineffective erythropoiesis and iron dysregulation. Epigenetic therapies that modulate the expression of fetal hemoglobin regulators, such as BCL-11A, and chromatin-modifying pathways may provide new opportunities to ameliorate disease severity. Nanomedicine could enhance the precision of delivery of gene-editing systems, RNA therapeutics, and iron chelators while minimizing systemic toxicity. Furthermore, stem-cell engineering, including the generation of genetically corrected autologous hematopoietic stem cells, together with personalized gene-editing strategies using CRISPR/Cas9, base editing, and prime editing, hold promise for durable and potentially curative treatments tailored to individual genetic profiles. Finally, combination therapies integrating gene-based interventions with pharmacological agents such as HbF inducers, erythroid maturation agents, hepcidin modulators, and iron chelators are likely to provide synergistic benefits, improving therapeutic efficacy and long-term clinical outcomes. Collectively, these innovations are expected to accelerate the transition toward highly personalized and potentially curative management of b-thalassemia.

9. Challenges

Despite remarkable progress in curated therapies, there are several challenges limiting their implementation in ß-

thalassemia. The genetic heterogeneity of mutations in HBB and modifier gene complicates genotype-phenotype correlations and selection of individualized treatments. The high cost and limited availability of advanced molecular diagnostics, gene-therapies and genome-editing technologies remain major barriers, particularly in low- and middle-income countries where disease burden is higher. In addition, long-term safety and durability data for emerging therapies, such as CRISPR-based gene editing, are still under development. On the other hand, there is need for standardized biomarkers, large multicentre validation studies, robust bioinformatics infrastructure, and integration of multi-omics and artificial intelligence into routine clinical practice. Ethical, regulatory and socio-economic issues, as well as disparities in access to healthcare also impede the worldwide implementation of approved therapies. To translate approved therapies into routine clinical care for patients with ß-thalassemia, collaborative research, technological innovation and equitable health care policies will be essential to overcome these challenges.

10. Conclusion

Precision medicine is transforming the treatment of ß-thalassemia from an indiscriminate treatment to a personalised treatment based on genetic, molecular and clinical features. Molecular diagnostics, modifier gene analysis, pharmacogenomics, targeted therapies, gene therapy, genome editing and computational approaches have significantly improved disease stratification and therapeutic outcomes while reducing transfusion burden and iron related complications. Despite challenges related to cost, access, long-term safety and clinical implementation, continued advances in genomics, multi-omics, artificial intelligence and stem cell technologies are likely to further enhance personalized approaches. Ongoing research and collaboration, hope that precision medicine can transform ß-thalassemia from a lifelong transfusion-dependent disorder into a manageable and, ultimately, curable disorder.

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