Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 9672 - 9678
Received 25 April 2021; Accepted 08 May 2021.

Current and Future Therapies in Thalassemia: Beginning of a New Era

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Abstract

Background

Thalassemia is a group of blood disorders that affect the hemoglobin genes and cause erythropoiesis to be ineffective. Anemia occurs early in life as a result of reduced hemoglobin development, necessitating regular blood transfusions to sustain hemoglobin levels. This activity explains the diagnosis and treatment of Thalassemia and stresses the importance of collaborating as part of a multidisciplinary team.

Objective

In this review an overview of Thalassemia along with various novel therapeutic approaches that are currently in development are discussed.

Method

Articles for the review were looked into sources like Pubmed, Google Scholar, Science Direct and Web of Science using the relevant search terms.

Result

Blood transfusions, drug treatment, and a bone marrow transplant are all required for people with serious Thalassemia. Patients with Thalassemia also depend on novel agents as their only remedy. Thalassemia gene therapy is currently being tested and may be available in the future.

Conclusion

Despite improvements in transfusion procedures and chelation therapy, there are still many hurdles to delivering these traditional therapies. The complexities of commonly available standard treatment and improvements in our knowledge of the fundamental path physiological processes in Thalassemia have spurred research into new therapeutic goals.

Keywords: Current, Future Therapies and Thalassemia

Introduction

Thalassemia are a complex group of genetic diseases caused by a drop in hemoglobin alpha or beta chain synthesis (Hb). The oxygen-carrying portion of red blood cells is hemoglobin. It is made up of two proteins, one alpha and the other beta. When the body doesn't produce enough of either of these two proteins, red blood cells don't develop properly and can't hold enough oxygen, resulting in anemia that can occur in infancy and last a lifetime [1]. Alpha thalassemia is induced by the deletion of the alpha-globin gene, which results in diminished or missing alpha-globin chain output. The alpha globin gene has four alleles, and the nature of the disorder depends on how many alleles are deleted [2]. Point mutations in the beta-globin gene cause beta thalassemia. The zygosity of the beta-gene mutation splits it into three groups. Beta-thalassemia minor is caused by a heterozygous mutation, in which beta chains are under produced [3].Thalassemia is autosomal recessive, which means that all parents must be carriers or have the disorder in order for it to be passed on to the next generation. It's caused by Hb gene mutations or deletions, which result in underproduction or the absence of alpha or beta chains. About 200 mutations have been identified as the cause of thalassemias. Deletions in the thalassemia gene cause alpha thalassemia. Alpha thalassemias are caused by deletions of alpha-globin genes, whereas beta thalassemias are caused by a point mutation in the beta-globin gene's splice site and promoter regions on chromosome [4].

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2. Epidemiological Overview

Alpha thalassemia is more prevalent in Asian and African populations, while beta thalassemia is more common in Mediterranean populations, but it is also be present in Southeast Asia and Africa. The incidence in these places may be as high as 10% [5]. Since there is no reliable screening system in use in the United States, the true number of thalassemia cases is uncertain. In India, Thalassemia and sickle cell diseases are a big health problem. According to the Census of India 2011, the average prevalence of thalassemia carriers is 3–4%, which corresponds to 35–45 million carriers in multi-ethnic, culturally and linguistically diverse population of 1.21 billion people, which also includes about 8% of tribal groups. Several minority groups had a slightly higher prevalence (4–17%) [6,7].

Within small geographic areas, minimal micromapping has shown an unequal distribution of thalassemia carriers in various districts in Maharashtra (1–6%) and Gujarat (0–9.5%). The predicted annual births of Thalassemia major babies in each district in these two states were also estimated. In Maharashtra, the average of homozygosity per 1000 births was 0.28, and in Gujarat, it was 0.39 [8,9]. HbE is more common in the north-eastern and eastern areas, with carrier frequencies ranging from 3 to over 50% in many groups, while HbS is more common among scheduled tribes, scheduled castes, and other backward castes, with carrier frequencies ranging from 5 to 35 percent in many groups [10]. According to figures, there are approximately 100,000 thalassemia patients and 150,000 cases of sickle cell disease in this vast region. However, the precise figures are unclear due to the lack of national patient registries [11].

3. Screening and Diagnosis

In general, the thalassemia screening and diagnostic algorithm can be split into two levels: population and person, with separate methods used based on the screening objectives [12]. The introduction of thalassaemia screening and preventive services is now universal, with geographic dissemination and cultural influences affecting their adoption. Screening services have been introduced across the world, as well as premarital and neonatal screenings. Analysis of WBC's combined with haemoglobin electrophoresis is needed to validate a thalassaemia diagnosis, with DNA analysis required to confirm the diagnosis of thalassaemia and haemoglobin [13,14].

4. Approaches towards Thalassemia

Standard remedies for Thalassemia include daily transfusions and iron-chelating medications, pharmaceutical activation of the globin gene, allogenic transplantation, or a single-dose cure in the form of gene therapy that does not require immunosuppressant [15].Three potential approaches to thalassemia treatment are: 1) Novel agents, 2) Gene-therapy approaches, and 3) Stem cell transplant advances.

4.1 Novel Approach Targeting Ineffective Erythropoiesis

The characteristic of Thalassemia is inadequate erythropoiesis due to globin chain mismatch. Anemia, hypoxia, and a reactive rise in erythropoietin (EPO) development are all signs associated with peripheral hemolysis, which contributes to bone marrow hyperplasia, extramedullaryhematopoiesis, and hepatosplenomegaly. Improved anemia, decreased splenic size and extramedullary expansion, indirect improvement in serum hepcidin, and improved QoL are all possible advantages of this approach [16].Agents that improve erythropoiesis, either directly as EPO or indirectly by inducing HbF synthesis, have been researched for decades. The recorded responses, on the other hand, were highly variable and volatile. Furthermore, these extended early precursors produce higher levels of the TGF-b ligand, growth differentiation factor 11 (GDF11), which prevents erythroid progenitor terminal maturation and the development of new red cells, contributing to a vicious loop of inadequate erythropoiesis in thalassaemia [17,18].

4.1.1 Induction of Erythropoiesis

In medicine, parenteral administration of recombinant proteins to treat pathological diseases is widespread. However, these procedures are typically costly and necessitate long-term patient compliance [19]. Anemia in people with advanced-stage progressive kidney failure, is treated with recombinant erythropoietin (EPO) injections on a daily basis, a procedure that costs thousands of dollars per year. Furthermore, there is a serious lack of donor organs, which is worsened by an ageing population, causing people to live with dysfunctional kidneys for much longer [20,21].

4.1.2 Use of Fetal Hemoglobin

Patients of Thalassemia who have persistently elevated levels of fetal globin have less serious anemia, milder clinical syndromes, and are mostly transfusion-free [22].Hydroxyurea (HU) is a compound that inhibits the development of HbF. Prescription of HU is suggested in Sickle cell disease (SCD) treatment because it has the capacity to induce globin gene expression and reduce expression of globin gene, as well as its anti-sickling

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effect [23].Furthermore, HU prevents vascular occlusion in these patients by reducing the number of white blood cells and blocking their activation. The efficacy of HU in treating patients with -Thalassemia major and intermedia has been disappointing, and the anemia has not improved substantially [24]. In particular, the cytotoxic effects of this medication allow the erythroid sequence to regenerate, and the metabolic effects cause nitric oxide (NO) to be released [25].

4.1.3 Role of Jak2 Inhibitors

Several activities, including cytokine signalling and cell-cell interactions, are closely regulated during erythropoiesis, especially in the form of erythroblastic islands, a specialized niche for the maturation of erythroid progenitors [26]. Activation of Jak2 results in the activation of the signal transductor and transcription activator Stat5 a and b, as well as simultaneous signalling pathways [27].Jak2 inhibitors could potentially minimize ineffective erythropoiesis (IE) by improving the equilibrium between proliferation and differentiation. Jak2 inhibition increased IE and decreased splenic size in thalassemia mouse models, but at the expense of decreased overall erythropoietic function, which was not improved by blood transfusion [28].Data from a phase 2a study indicate that ruxolitinib decreases splenomegaly in thalassemia patients, suggesting that inhibiting the EPO-EPOR-JAK2-STAT5 axis can restrict the overproduction of erythroid progenitors in the spleen [29].

4.1.4 Sotatercept and Luspatercept Agents

For the treatment of IE-related disorders, two medications were developed: Sotatercept (ACE-011) and Luspatercept (ACE-536). Sotatercept is a recombinant human homodimericactivin type IIA receptor fusion protein made up of the human activin type IIA receptor's extracellular domain fused to the human immunoglobulin G1 Fc domain [30].Luspatercept is a human activin type IIB receptor-specific recombinant fusion protein. Luspatercept binds to TGF-beta superfamily ligands with high affinity, such as GDF11 and GDF8 [31].Further study indicated that sotatercept and luspatercept improve anemia in conditions characterized by inadequate erythropoiesis, such as Thalassemia and myelodysplastic syndromes, by reducing Smad-2/3 signaling (MDSs) [32].

4.1.5 Forkhead-Box-Class-O3

In the early stages of erythropoiesis, the transcription factor forkhead-box-O3 (Foxo3) defends the cell from oxidative stress by upregulating antioxidant enzymes. The EPOR-pI3K/AKT/mTOR signalling pathway phosphorylates Foxo3 and it is translocated out of the nucleus, where it remains inactive [33,34].As a possible Fetalhemoglobin (HbF) inducer, Foxo3 activation could help enhance anemia in thalassemia patients. Its function in hemoglobinopathies, however, is still unclear [35,36]. Metformin, a diabetes type 2 treatment, is a Foxo3 inducer. A current phase 1 clinical trial in adults with sickle cell anemia and NTDT is looking into its use as a HbF inducer [37]. These agents are currently in preclinical testing and need to be tested further.

4.2 Novel Approach Targeting Iron

Hepcidin, a hormone produced in the liver, controls the distribution of iron, which is necessary for erythropoiesis. Hepcidin production and secretion are impaired by IE and chronic hypoxia. In Thalassemia, an abnormally low hepcidin level improves duodenal iron absorption [38].

4.2.1 Role of Mini - Hepcidin

Mini-hepcidins are peptide mimics that are long enough to cause hepcidin actions, lowering serum iron levels and alleviating iron overload. In Hbbth3/l mice, these compounds dramatically reduce iron overload and erythroid cell damage [39].Another option is to improve hepatic hepcidin synthesis by inhibiting TMPRSS6, a transmembrane serine protease (matriptase-2) that usually inhibits hepcidin synthesis by deactivating hemojuvelin. In a mouse model, deleting the TMPRSS6 gene enhanced hepcidin expression, improved anemia, and decreased IE, splenomegaly, and iron loading [40].

4.2.2 Apo-Transferrin Administration

In Thalassemia, reduced transferrin saturation can be helpful, so Apo-transferrin administration can lower labile plasma iron concentrations, normalize RBC survival, and improve Hb production. Clinical trials for this protein are also in the early stages [41, 42].

4.3 Gene therapy

The age of genome sequencing and understanding of the Hemoglobin Subunit Beta (HBB) gene cluster, as well as its tight regulation and control, has brought thalassemia patients new treatment choices. The full understanding of the transition from g-globin to b-globin, as well as how different transcription factors (TF)

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regulate this switch, has provided new targets for gene alteration [43, 44].Gene-therapy approaches are currently classified into two categories: Gene addition and Gene-edition.

4.3.1 Gene addition

After myeloablation, a lenti-viral/retroviral vector carrying the entire regulatory and bor gproducing genes is injected into autologous human stem cells in vitro, and the transformed stem cells are infused back into the patient [45].In general, gene therapy includes isolating HSC, modifying the defective gene ex vivo, a myeloablative conditioning regimen, and reinfusion of sufficiently genetically engineered HSC to repopulate the hematopoietic compartments [46].The initial results of two parallel trials (HGB 204 and 205 using the BB305 vector) show that the gene-insertions contain an average of 4-5 g/dl of HbA^{T87Q}.In HbE/b-thalassemia, a 5 g/dl rise in Hb is enough to gain transfusion freedom [47]. The efficiency of stem cell transduction is being increased by technical advances.

4.3.2 Gene editing

Modulation of globin gene regulators attempting to facilitate chain synthesis has been used as another method as understanding of the molecular mechanisms regulating globin gene expression has grown [48].Several nucleases, including engineered zinc fingered nucleases (ZFN), transcription activator-like effector nucleases (TALEN), and clustered frequently interspaced short palindromic repeats connected to Cas9 nucleases, were used in the editing method (CRISPR-Cas9) [49].BCL11a (the transcription factor that governs the transition from HbF to HbA) is an excellent candidate for gene-editing techniques. It is thought that by inhibiting BCL11a, thalassemia patient's HbF development can be reactivated [50].Animal trials are currently being undertaken to determine which of these approaches and targets result in substantial HbF output with limited toxicity to stem cells and off-target activity. Many of these approaches are expected to reach clinical trials in the near future, after they have been developed and scaled up to human implementations. They will dramatically boost the conditions of thalassemia patients if they are shown to be efficacious, healthy, and long-lasting [51].

4.4 Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is an example of medical innovation that has grown and changed rapidly in the last two decades. It's a time-consuming and expensive procedure that relies on a well-established institutional infrastructure network [52, 53]. For patients with Thalassemia, HSCT from a well-matched donor remains the traditional curative alternative [54, 55]. Unrelated organ transplants, cord blood transplants, and haplo-identical transplants are all novel ways to expand the donor population right now [56].Unrelated organ transplants, cord blood transplants, and haplo-identical transplants are all novel ways to expand the donor population right now [57, 58].Each of these options should be explored further in well-designed trials with endpoints that include not only transfusion freedom, but also quality of life, iron overload, and HSCT-related morbidity. HSCT-related complications such as graft versus host disease (GVHD) have an impact on iron overload and associated morbidity in the post-transplant era [59, 60].

5. Conclusions

Many of these potential treatments are unlikely to work for all thalassemia patients due to genotype/phenotypic heterogeneity, but combination therapies may improve outcomes and quality of life. In the future, it would be critical to combine different therapies based on a template based on their mode of action and non-overlapping toxicity. For better thalassemia care, a new era of novel therapeutics is emerging. Understanding of the underlying pathophysiological mechanisms spark's research into the development of new therapeutics. Future clinical trials are needed to determine the best way to use these new therapeutic alternatives as monotherapies, sequentially, or in combinations.

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