ABSTRACT

The thalassemia is a diverse group of hereditary disorder in which there is a reduced rate of synthesis of one or more of the globin polypeptide chains. Thus, thalassemia, unlike hemoglobinopathies which are qualitative disorder of the hemoglobin, are quantitative abnormalities of polypeptides globin chain synthesis. Normally an individual inherits two β-globin genes located one each on two chromosomes 11, and two alpha globin genes one each on two chromosome 16, from each parent i.e. normal adult hemoglobin is α2β2. Thalassemias are particularly associated with people of Mediterranean origin, Arabs and Asians. gives the information of a survey in thalassemia center it reveals the information that majority of patients are undergoing blood transfusion when compared to bone marrow transplantation because it is a risky procedure. Gene therapy is an exciting prospect, although, there are still formidable obstacles to be overcome before it is likely to become feasible for the thalassemics. Deliveries of transgenes in stem cell based gene therapy are effective in the therapeutic management. Thalassemias are diverse group of hereditary disorders in which there is a reduced rate of synthesis of one or more of the globin polypeptide chains. Current approaches include hematopoietic stem cell transplantation. Disease management includes prenatal diagnosis, transfusion therapy, bone marrow transplantation out of which only BMT is potentially curative.

Keywords: BMT, Gene therapy, Stem cells, Hereditary disorder.
management includes prenatal diagnosis, transfusion therapy, bone marrow transplantation out of which only BMT is potentially curative. The thalassemias are classified according to which chain of the hemoglobin molecule is affected. There are two main types of thalassemia.  

- Alpha thalassemia occurs when a gene or genes related to the alpha globin protein are missing or changed (mutated).
- Beta thalassemia occurs when similar gene defects affect production of the beta globin protein.

**Signs and Symptoms**

Severe tissue hypoxia  
Hemolytic anemia  
Iron overload  
Shortness of breath  
Bone deformities in the face  
Dark urine  
Slowed growth and delayed puberty  
Jaundice  
An enlarged spleen, liver, and heart

**Figure 1:** Statistical data of thalassemia

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>UAE NATIONALS</td>
</tr>
<tr>
<td>IR</td>
<td>IRANIAN</td>
</tr>
<tr>
<td>IN</td>
<td>INDIAN</td>
</tr>
<tr>
<td>OM</td>
<td>OMANI</td>
</tr>
<tr>
<td>PK</td>
<td>PAKISTANI</td>
</tr>
<tr>
<td>UC</td>
<td>UNCLASSIFIED</td>
</tr>
</tbody>
</table>

**Figure 2:** Pathogenesis of thalassemia
Molecular Pathogenesis

Each hemoglobin molecule contains four subunit proteins. Two of the subunit proteins are called alpha and two are called beta. Hemoglobin properly binds and releases oxygen only when two alpha subunits are connected to two beta subunits.\(^7,8\) A pair of genes located on chromosome #16 controls the production of the alpha subunits of hemoglobin. A single gene located on chromosome #11 controls the production of the hemoglobin beta subunit. Thalassemia occurs when one or more of the genes fail to produce protein, leading to a shortage of one of the subunits.

**Figure 3: Molecular pathogenesis**

**α-Thalassemia**

These are disorders in which there is defective synthesis of α-globin chains\(^9\) resulting in depressed production of hemoglobin that contains alpha chains i.e. HbA, HbA\(_2\) and HbF. Accordingly, alpha thalassemias are classified into four types

- Hb bar's hydrops foetalis
- HbH disease:
- α-thalassemia trait
- α-thalassemia trait (carrier)

**β-Thalassemia**

A defect in the production of beta globin protein from the beta genes is the most common cause of beta thalassemia. Most of β-thalassemias arise from different types of mutations\(^10,11\) of β-globin gene resulting from single base changes. Depending on the extent of reduction in β-chain synthesis, there are three types of β-thalassemia:

**Treatment and Management**

**Conventional Treatment**

- Blood Transfusion
- Iron Chelation

**Treatment of Complication**

- Infections
- Heart Failure etc.

**Cure**

- Bone Marrow and Stem Cells Transplantation
- Gene Therapy

**Blood Transfusion Therapy**

Regular blood transfusion program must be provided for those suffering anemia problems\(^12\) from severe beta-thalassemia diseases. The goal of transfusion therapy is to correct anemia adequate to maintain quality of life and normal development, suppress erythropoiesis and inhibit gastrointestinal iron absorption. The effectiveness of transfusion therapy should be monitored by recording the patient’s body weight, pre- and post-transfusion Hb and volume of blood units transfused and the transfusion interval

- Iron Chelation Therapy

The most profound adverse effect of regular blood transfusion\(^13,14\) is iron overload. To prevent continued accumulation of iron in tissues, iron
chelators need to be administered to facilitate removal of iron through faecal and urinary routes.

- **Bone Marrow Transplantation (Hematopoietic Stem Cell Transplantation)**

![Figure 4: Survival rate of HSC transplantation](image)

This modern procedure has been the only accepted method worldwide to cure β-thalassemia diseases by means of allograft transplantation. The major source of haematopoietic stem cells for transplant is still derived from HLA-identical sibling bone marrow. A blood and marrow stem cell transplant replaces faulty stem cells with healthy ones from another person.\(^{15}\)

**Treating complications**

An important part of managing thalassemias is treating complications; treatment\(^ {16}\) may be needed for heart or liver diseases, infections, osteoporosis, and other health problems.

- **Gene Replacement Therapy**

The transfer of a globin gene in autologous haematopoietic stem cells is an attractive treatment possibility. It poses challenges in terms of controlling transgene expression, which should be:

- Erythroid-specific
- Elevated
- Position-independent
- Sustained over time.

**Gene transfer using onco-retroviral vectors:**

![Figure 5: Gene transfer by retro viral vectors](image)

Recombinant onco-retroviruses were the first viral vectors used to transfer the human β-globin gene in mouse HSCs. Studies aimed at increasing expression\(^ {17,18}\) levels of transferred β-globin genes have focused on locus control region elements of the human β-globin gene locus into
onco-retroviral vectors. Incorporation of the core elements of HS2, HS3, and HS4 of the human β-globin LCR significantly increased expression levels in murine erythroleukemia (MEL) cells but failed to abolish positional variability of expression.

- **Gene transfer using lentiviral vectors**

Lentiviral vectors which stably transmit the β-globin expression cassette, offering new prospects for the manipulation of haemopoietic stem. The Lentiglobin vector is self inactivating and contains large elements of the b-globin locus control region as well as chromatin insulators and other features that should prevent untoward events. The original studies in mice showed that lentiviral-mediated human β-globin gene transfer can rescue mice affected by β-thalassemia intermedia and β-thalassemia major.

**Gene correction and induced pluripotent stem (iPs) cells**

The only cells that are amenable to gene targeting and correction, which requires unlimited in vitro cell division without losing multipotency, are the embryonic stem cells. Cells obtained by this reverse-differentiation process, called induced pluripotent stem cells. Subsequently, the iPS cells were differentiated into hematopoietic cells that synthesized hemoglobin. Therefore, in the future the mutation in the β-globin gene of these iPS cells could be corrected by gene targeting.

**Splice-switching and stop codon readthrough**

Defective β-globin gene expression and β-globin deficiency can be attributed to almost 200 thalassemic mutations. These mutations lead to incorrectly spliced mRNAs, even though the correct splice sites remain undamaged and potentially functional. Use of small nuclear RNA and splice-switching oligo-nucleotides can restore the corrected splicing re-establishing the synthesis of the normal protein. Another approach showing a great potential for the treatment of genetic disorders characterized by premature termination codons is the use of drugs to induce stop codon readthrough. These modified RNA would protect against nonsense-mediated mRNA decay and allow production of a protein.

**RESULT AND DISCUSSION**

Figure 1 gives the Statistical data of thalassemia where the affected people are higher in Arab countries. Figure 2 illustrate the pathogenesis of thalassemia where as Figure 3 gives the details of molecular pathogenesis of thalassemia. In Figure 4 the rate of survival of patients after bone marrow transplantation. As the graph gives the survival rate as it is a risky procedure to get a HLA-identical sibling bone marrow. Figure 5 give the information of gene transfer using retro viral vectors. Figure 6 shows the schematic representation of gene therapy.
The above Figure gives the information of a survey in thalassemia center it reveals the information that majority of patients are undergoing blood transfusion when compared to bone marrow transplantation because it is a risky procedure. Despite the increased life expectancy of thalassemia, complications keep arising. These relate to inadequate trans-fusions, transfusion transmitted viral diseases, allo-sensitization, iron overload related endocrine, liver and cardiac disturbances as well as toxicities of iron chelators. Gene therapy is an exciting prospect, although, there are still formidable obstacles to be overcome before it is likely to become feasible for the thalassemics. Deliveries of transgenes in stem cell based gene therapy are effective in the therapeutic management. Lentiviral vectors have an advantage over onco-retroviral vector due to integration of larger element and minimal sequence rearrangement. Induced pluripotent stem cells, splice-switching and stop codon read-through are other genetic approaches which are showing advantages over the current therapy.

CONCLUSION

Thalassemias are diverse group of hereditary disorders in which there is a reduced rate of synthesis of one or more of the globin polypeptide chains. Current approaches include hematopoietic stem cell transplantation. Disease management includes prenatal diagnosis, transfusion therapy, bone marrow transplantation; out of which only BMT is potentially curative. As thalassemia is genetically derived disorder, genetic and cellular targets are potential approaches in management of disease.

ACKNOWLEDGEMENT

The authors are very much thankful to Management and principal of KVSR Siddhartha College of pharmaceutical sciences, Vijayawada for their support and constant encouragement.

REFERENCES