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Pharmacogenomics of the Drugs used for the Treatment of Thalassemia

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Abstract

Thalassemia is one of the most prevalent inherited blood disorders all over the world. There are some specific hematologic tests and molecular genetic techniques known for diagnosis of thalassemia. Nowadays, various types of drugs are used for the treatment of thalassemia. Hydroxyurea, Hydroxycarbamide, Deferiprone, Deferisirox, Butyrate and its derivatives are some of the most common and well known drugs which are used for increasing the HbF percentage and iron chelation. Pharmacogenomics is the branch of pharmacology that is associated with the influence of genetic variations on the drug response among patients by correlating genetic variations, expression pattern or single-nucleotide polymorphisms with a drug's efficacy or toxicity. With the help of Pharmacogenomics study "personalized medicine" has been explored, in which drugs and drug combinations are optimized for the genetic makeup of each individual.

Introduction

Thalassemia is an inherited autosomal recessive blood disorder. It is widely defined as the syndrome which is caused by reduced or absent synthesis of globin chains. It is also formed by certain abnormal hemoglobin variants that are nonfunctional in nature and very unstable so that proper function of globin chain is disturbed [1]. Production of deformed globin chains leads to the problem of imbalance in between α and β globin chains. Due to cross - racial marriage and high migration rate thalassemia is now found throughout the world, but mostly it is common in Mediterranean countries, few parts of tropical and sub-tropical regions including South East Asia, Southern China, Indian subcontinent. Majority of the affected births are reported from low income developing countries due to lack of proper knowledge, awareness and health facilities [2]. Throughout the world nearly 3% population are the carrier for thalassemia [3]. Thalassemia is mainly of 3 types according to the clinical severity, thalassemia major, intermedia and minor. Blood transfusion is the essential requirement for survival of thalassemia major patients. Cardiac problems, hepatomegaly, spleenomegaly, increased vascular stiffness are often found to be associated with the transfusion dependent major patients as the adverse effect of iron overload. As the body has no such means to eliminate excess iron, iron chelators are prescribed that help to excrete free iron through urine and/or stool. Deferiprone, Deferasirox are some well-known iron chelators which are generally used for reducing the iron overload among the thalassemia patients. Increased expression of fetal hemoglobin (HbF) can improve the clinical course of thalassemia. There are certain pharmacological agents eg.-Hydroxyurea (HU), Hydroxycarbamide (HC), 5'-Azacytidine (5'-Aza) which help in augmenting HbF level. It has been reported that nearly 25% of Hydroxyurea and Butyrate treated thalassemia patients fail to respond [4]. So there must be some correlation in between the individual genetic constitution with response and tolerance to commonly used drugs for the treatment purpose. Recently the Genome Wide Association Studies (GWAS) have been implicated upon thalassemia patients in different parts of the world and it gives the knowledge about the genetic variants/polymorphisms which exerts the positive effect on elevation of HbF level when treated with prescribed drugs [5].

Pharmacogenomics of HbF Elevating Drugs

There are several drugs responsible for inducing the γ globin gene expression among thalassemia patients like Hydroxyurea (inhibitor of Ribonucleotide Reductase), Sodium Butyrate (inhibitor of Histone Deacetylase), 5'-Azacytidine (DNA Methylating agents) [6]. These drugs help to improve α:β ratio in the erythroid progenitor cells and thus improve the major complication among transfusion dependent thalassemia major patients [7].

Hydroxyurea

Hydroxyurea (HU) is considered as an inducer of HbF production. The successful use of Hydroxyurea (HU) for HbF elevation is influenced by the genetic variants of individual thalassemia patients. The substitution of C to T at -158 Gγ genes in the Xmn1 polymorphic site has a positive effect on Hydroxyurea treatment for the production of Hb F by inducing Gγ gene [8]. The molecular mechanism behind the role of Xmn1 polymorphic site in the induction for HbF production is still unknown [9]. Among the five common mutations in Indian population [codon 8/9 (+G), codon 41/42(-TCTT), IVS1-1 (G>T), IVS 1-5 (G>C), 619 bp deletion] the IVS 1-1 (G>T) mutation and Xmm 1 homozygous (+/+) mutation is greatly associated with the increased production of HbF after Hydroxyurea treatment. Increased HbF levels upon treatment with HU was also seen in patients with Xmn-I polymorphism and IVS II-I mutation [10]. There are several genetic variants situated at the promoter and intronic region of MAP3K5 and PDE7B gene (chromosome 6q23). These genetic variants play crucial role in regulating HU response among β-thalassemia patients [11]. Another study done on the HbE/β0-

thalassemia patients of Asian origin revealed that polymorphism in rs 2071348 (g.5264146 A>C) on HBB pseudogene (HBBP1) can be used as the pharmacogenomic marker for HU treatment efficacy [12]. The polymorphism of SAR1A may be a key regulator for differential response of another HU derivative hydroxycarbamide among thalassemic patients. SAR1A encodes a GTP-binding protein that has been reported to have regulatory role in induction of the gamma globin gene [13]. Loci situated on chr 6q and 8q are associated with HC metabolism [14].

Butyrate and its derivatives

Butyrate derivatives are histone deacetylase (HDAC) inhibitors and helps the augmentation of fetal haemoglobin. In a study undertaken in Canada, good response has been reported after treatment with Butyrate. Among them most of the β-thalassemia major patients had mutation in -28 TATA box, A>G and HbE/β thalassemia patients with mutations at codon 17(A>T) and codon 26(G>A) [15]. Those patients who are compound heterozygote for the nonsense mutatation of codon 37 and -86 (C>G) mutation are the well responder for Oral isobutyrate (IBT) drug. Patients having homozygous mutation for nonsense mutation of Codon 39 that leads to inactivation of affected gene give satisfactory result after treatment. Moreover the presence of β-thalassemia mutations like IVS1 +110(G>A), FS8/9(+G), IVS2 +745(C>G) also facilitates the drug metabolism among the patients [16]. It has been reported that Decitabine, Butyrate derivatives has good therapeutic effects in patients with sickle cell anemia, even in patients resistant to HU [17].

Iron Chelating Drug

In case of thalassemia major patients, the iron binding capacity of transferin and ferritin protein in blood is exceeded; the free iron starts to accumulate in different organs and can cause oxidative tissue damage. Iron chelation therapy is essential for those thalassemic patients receiving blood transfusion regularly.

Deferasirox

Deferasirox is a tridentate oral iron chelator. The presence of any inducers of UDP-Glucuronasyl transferase leads to decrease the activity of Deferasirox (DFX) [18]. So any genetic variations within the inducer genes can influence DFX activity. It has been observed among many paediatric patients that there are nearly 20 genetic polymorphic sites which are associated with differential DFX metabolism, breast cancer resistance protein [BCRP] 34G>A, 8191C>T, 8825C>A; Multidrug Resistance Associated Protein 2 [MRP2]: -1774 del G,-24C>T; UGT1A7[UDP-Glycuronosyl transferase 1A7]: 387 T>G, 391C>A, 392G>A, 622 T>C and UGT 1A9(-118 ins T) [19]. The genetic polymorphism within CYP1A1, CYP1A2, CYP2D6 have role in metabolism of Deferasirox. It has been reported that CYP1A1C>A rs2606345 AA, CYP1A2 C>T rs 2470890 TT genotypes may have some negative role in DFX efficacy [20].

Deferiprone

Deferiprone is a bidentate another oral iron chelator. Deferiprone is metabolized into deferiprone-3-0-glucuronide (DG) by the enzyme UDP-glucuronosyl transferase (UGTs). UGT belongs to two gene families viz.UGT1 and UGT2. Among several isoforms of UDP-glucuronosyltransferase few are well known, viz.UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B15 [21]. The

UGT1A and UGT2B are responsible for glucuronidation of deferiprone [22]. Two variants,-2152 C>T and -275 T>A in the promoter of UGT1A9 gene are associated with the increased expression of UGT IA9. The UGT1A9 can also perform the glucuronidation of deferiprone. Thus the affectivity of deferiprone may influenced by those genetic variants. It has been known that there are three most commonly known polymorphisms in UGT1A6 like Thr181Ala (541 A>G), Arg 184 Ser (552 A>C) and Ser 7Ala (19T>G); these are responsible for the efficacy of deferiprone treatment [23].

Deferoxamine

Deferoxamine is a hexadentate iron chelator, which is administered subcutaneously or intravenously. After administration of deferoxamine, the survival rate was found to be progressively increasing for every 5-year birth cohort since 1975, the year of introduction of deferoxamine as iron chelator [24]. But, due to inconvenience of administration of deferoxamine, there is decreased efficacy in terms of iron chelation and progression of the manifestations of transfusional iron overload [25].

Conclusion

Pharmacogenomics study becomes an essential part in modern medical practice. This branch of science is important for assessing the drug efficacy and toxicity. It facilitates the rationality of drug invention and application for genetic diseases like thalassemia. Thalassemia being genetic disease cannot be cured permanently by using a particular drug. Clinical severity can be declined by using drugs that help in increasing the production of HbF or by removing the excess amount of iron from body. There are several innovative therapeutic aspects which have been proposed but still need to be applied clinically. One of these novel therapeutic approaches for the treatment of β-thalassemia is the transfer of normal human β-globin gene in autologous hematopoetic stem cell of the thalassemia patients [26]. Though, transplantation can lead to thalassemia free survival, the rate of mortality due to allogenic rejection of hematopoietic stem cell transplantation. Now a day's several studies on genomics and proteomics are going and these may be helpful in improving the treatment of β-thalassemia. There are some patients who respond to certain drugs, at the same time some patients manifest different side effects; the exact reason behind differential clinical response for any drug among thalassemia patients is still under research. Population specific genome studies have already delivered some results about this aspect [27].

Although many HbF inducing drugs are available for treatment purpose, HU is widely used for long term application. Some of the drugs are known to have carcinogenic and mutagnic effects. Among the iron chelators, Deferaoxamine sometimes exhibits neurotoxicity, growth retardation and visual problems after prolonged use [28]. Many researches are going on to target EKLF1 (Erythroid Kruppel Like Factor 1), BCL11A, HBSIL-MYB genes which are known as HbF modulators. Besides miRNAs (miRNA 144) are now in trial to prevent the precipitation of α-chain. Epigenetic modifications within the signalling pathway may play significant role in increasing HbF level by regulating γ-globin gene expression. Investigations on these genetic elements may give some clues for preventing the harmful side effects of drugs during treatment [15]. Recent experimental evidences suggest that there are several genetic variants situated on modifier genes residing on outside the β-globin gene cluster which regulate the differential response for a particular drug. So, it is really fascinating

and challenging to explore different dimensions in the branch of pharmacogenomics. There are very few reports so far available for the usefulness of pharmacogenomics in treating thalassemia [29]. Researchers are now trying to find out the association between drug efficacy and genotype of patients. Study on Pharmacogenomics will help in future to develop personalised medicine for Hb F elevating drugs, chelating agents that may provide the optimum physiological requirements to maintain the smooth and normal life of thalassemia patients.

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