Targeted Fetal Hemoglobin Induction for Treatment of Beta Hemoglobinopathies

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KEYWORDS

• Fetal hemoglobin • Genetic modifiers • Sickle cell disease • Beta-thalassemia • Stress signaling

KEY POINTS

- Fetal globin reduces clinical events initiated by sickle hemoglobin polymerization, because it cannot participate in the process.
- Fetal globin chains reduce excess alpha globin and globin chain imbalance in β-thalassemia, improving total hemoglobin levels.
- Target levels of fetal globin that reduce clinical severity in sickle cell disease and β-thalassemia are established from natural mutations, modifiers, and from treatment trials.
- Genetic modifiers related to the beta globin locus and/or to erythroid cell stress signaling and survival influence responses to different therapeutics.
- Combinations of therapeutics with differing molecular mechanisms and that promote erythroid survival offer new opportunities for personalized, highly active treatment.

INTRODUCTION

β-Thalassemia syndromes are common monogenic disorders worldwide, characterized by molecular mutations that cause deficiency of the beta globin chain of adult hemoglobin (HbA; $\alpha_2\beta_2$), and an excess of unmatched alpha globin chains.[1–8] Excess

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alpha globin damages the red blood cell membrane and causes apoptosis of developing erythroblasts and intramedullary hemolysis.[1–8] Clinical observations and previous trials of fetal globin inducers have shown that patients with β-thalassemia benefit from natural persistence of, or pharmacologic induction of, another type of globin that is normally suppressed before birth and in infancy: fetal hemoglobin (HbF; HBG, gamma globin).[1–20] Patients with higher gamma globin levels than their counterparts with the same mutations often do not require transfusions as regularly or as early in life as patients with lower levels of gamma globin. Inheritance of a single modifying trait that increases HbF, such as a single nucleotide polymorphism (SNP) in BCL11A, without any other genetic difference, can produce higher total hemoglobin up to 1 g/dL.[21] The impact of HbF is particularly notable in infants with sickle cell disease (SCD), who survive in utero in a highly hypoxic environment that would produce completely sickled cells with no oxygen delivery without the presence of HbF in every red blood cell. Other natural models of the benefit of increased HbF include sickle cell populations with milder disease and greater than or equal to 20% HbF in Saudi Arabia and in India (the Arabian Indian haplotype), whereas 30% HbF in S-HPFH produces a benign condition. The National Institutes of Health Natural History Study and multiple studies of hydroxyurea (HU) showed the highly significant ameliorating effects of HbF at levels greater than 8.6% or 0.5 g/dL.[22–26] In addition, treatment trials, such as those conducted with arginine butyrate, have increased HbF from a mean of 7% to 21% and reduced hospital days by 3-fold.[15] Inducing gamma globin expression by even small increments is recognized as a therapeutic avenue that should be amenable to broad application, because the gamma globin genes are universally present and normally integrated in hematopoietic stem cells.[1,2,27] Although a single chemotherapeutic drug, hydroxyurea, is commercially available and has had variable effects, several important principles for this approach have been defined in trials of prior generations of therapeutics.[22–27] The recent discovery of new therapeutic candidates now offers a renaissance for this approach.

EXPERIENCE IN TRIALS OF PRIOR GENERATION HBF INDUCERS

Table 1 lists several therapeutics that induce HbF and are being clinically investigated. Proof of principle of HbF induction was shown in previous clinical trials of several drugs in which pharmacologic reactivation of gamma globin expression reduced anemia and even eliminated transfusion requirements in patients with β-thalassemia.[27] HbF induction has been accomplished with chemotherapeutic agents, particularly 5-azacytidine, and 5-aza-2-deoxycytidine (decitabine),[14–20] and with short-chain fatty acids (SCFAs), such as arginine butyrate (AB) and sodium phenylbutyrate.[2,9,10,12,13,15,28] 5-Azacytidine and decitabine have shown high potency with responses in 12 of 13 patients in one study, including adult patients with SCD who do not respond to hydroxyurea.[17] Cellular abnormalities were all reduced after HbF levels were increased.[17]

A therapeutic that is not cytotoxic is preferable for a long-term therapy in β-thalassemia, because with cumulative dosing with hydroxyurea total hemoglobin (Hgb) levels increase, usually by less than 1 g/dL but also tend to decline over time.[16,17] The first-generation SCFAs had limitations of rapid metabolism and high dose requirements; AB and phenylbutyrate are also global histone deacetylase (HDAC) inhibitors that inhibit erythropoiesis through cell cycle arrest.[2] Erythropoiesis-stimulating agents are beneficial, but require parenteral administration and are too costly for lifelong therapy.[19,29–32] Nevertheless, these three classes of therapeutics reduced anemia and rendered some patients with thalassemia transfusion independent.[2,9,10,27] Therapeutics that require lower doses and oral administration would allow broader application,