Life Sciences 178 (2017) 100–108

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Therapeutic strategies in Sickle Cell Anemia: The past present and future

Queenie Fernandes *,[1]

University of Greenwich, United Kingdom

ARTICLE INFO

Article history:
Received 25 January 2017
Received in revised form 22 March 2017
Accepted 22 March 2017
Available online 20 April 2017

Keywords:
Sickle Cell Anemia
Sickle Cell Therapeutics
Sickle Cell Research
Hemoglobinopathies

ABSTRACT

Sickle Cell Anemia (SCA) was one of the first hemoglobinopathies to be discovered. It is distinguished by the mutation-induced expression of a sickle cell variant of hemoglobin (HbS) that triggers erythrocytes to take a characteristic sickled conformation. The complex physiopathology of the disease and its associated clinical complications has initiated multi-disciplinary research within its field. This review attempts to lay emphasis on the evolution, current standpoint and future scope of therapeutic strategies in SCA.

Contents

1. Introduction

Sickle Cell Anemia (SCA) arises out of a point mutation in the bases coding for the sixth amino-acid of the β-chain of hemoglobin. A single nucleotide substitution from GTG to GAG causes the amino acid valine to replace glutamic acid in the growing protein chain. This altered translational event gives rise to a mutant variant of hemoglobin (HbS) with different properties than the wildtype hemoglobin (HbA) molecule. Under deoxygenated conditions, HbS molecules tend to aggregate into long rigid chains that distort the shape of the erythrocytes causing it to take up its characteristic sickle-shaped conformation.

This sickling event remains to be the underlying cause for a trail of associated clinical complications. Its principal & mechanism of occurrence has inspired multi-disciplinary research, commencing right from the origin and discovery of the SCA mutation.

2. Evolution of therapeutic strategies targeting SCA

SCA has been a common genetic disorder that has prevailed over centuries with the highest incidence in Sub-Saharan Africa and the

* Corresponding author.
E-mail address: Queenie.Fernandez@gmail.com.
[1] Current Address: National Center for Cancer Care and Research (NCCCR), Hamad Medical Corporation, PO Box; 4572 Doha, Qatar.

http://dx.doi.org/10.1016/j.lfs.2017.03.025
0024-3205/

Caribbean. It is said to have originated among African and Afro-American populations.

The co-occurance of the disease among generalized African populations during a period of endemic malaria sparked an interest to determine whether the two diseases were linked by a selective advantage.

In 1949, J.S.B. Haldane popularized a theory stating that infectious diseases may be a driving force of natural selection [1]. In accordance with this theory, Haldane suggested that patients with the β-thalassemic mutation showed an increased fitness or resistance to malaria. Later in 1954 these findings were confirmed when A. C. Allison stated that Sickle cell heterozygotes have considerable protection against malaria [2].This protective effect thus brought about an equilibrium in which the homozygotic hemoglobinopathic disadvantage was balanced by a heterozygotic advantage offering protection against malaria [3]. Currently this hypothesis has been accepted and supported by a number of studies [4–9]. Certain other, studies state that the SCA mutation does not offer direct protection from the malarial parasite (*Plasmodium falciparum*) but instead deters progression to clinical malaria by improving clearance of infected erythrocytes thereby interrupting parasite growth [10].

Moreover, certain ancient African beliefs associated with the disease emphasized that the disease was a curse from tribal Gods. No later, a common myth originated in Nigeria; according to which the disease affected only children that are reincarnated [11].

However, the onset of medical research and the development of novel diagnostic techniques, led researchers to unveil the true cause and nature of the disease through a series of milestones (Table 1).

Sickle cell hemoglobin (HbS) was first detected in the blood stream by James Herrick in 1910. Subsequent research initiatives over an extensive period of time were inefficient in identifying factors that caused the disease. A major breakthrough along these lines was brought about by Ingram (1957) [12], who unraveled the mutational mechanics underlying the disease and its resultant expression of the mutated protein (HbS).

Early investigations began with a study [13] in 1948 where it was first noted that the symptoms of SCA appeared in infants only after levels of fetal hemoglobin (HbF) began to fall and be replaced by adult hemoglobin. This substantiated a theory that fetal hemoglobin proved advantageous over the sickle cell trait, which paved the way for a series of experiments targeting the increase of fetal hemoglobin in the blood. Hydroxyurea was one such drug that was found to trigger the expression of fetal hemoglobin in adults. However, it was only in 1998 that the Food & Drug Administration (FDA) approved the use of hydroxyurea in the treatment of adults with Sickle Cell Anemia. However its application in therapy was still controversial due to its reported toxicity in a number of cases [14,15].

Further reports stated that polymerization of hemoglobin initiates due to an increased permeability of the erythrocyte membrane [16]. This permits the entry of calcium ions and the loss of potassium ions and water leading to severe dehydration and rigidity of the red blood cells. Relevant therapeutic measures that could control cation homeostasis began to surface in the form of ion-channel blockers like Clotrimazole and ICA-17043 [17]. Although these received success in terms of decreasing membrane-permeability, they were unable to curb the painful crises associated with the disease and showed numerous fatal side-effects.

In another effort to conceptualise therapy, Hebbel, et al. [18] undertook a clinical trial with 33 patients diagnosed with Sickle Cell Anemia. Their work established a firm relationship between erythrocyte adherence to the endothelium and severity of the disease stating that higher the adherence greater the severity. This theory triggered the reasoning of an anti-adhesion treatment. Nearly two decades later, transcription inhibitors that facilitate down regulation of pro-adhesive molecules aiding erythrocyte adhesion began to surface. Solovey et al. [19] emphasized on the use of sulfasalazine as inhibitors of cell adhesion. Although sulfasalazine led the way to new dimensions in therapeutic advances, it was reported that patients regained symptoms once the steroid was discontinued.

Blood transfusion was also evaluated for possible corrective measures in SCA [20]. Apart from it being laborious, it is not generally practiced due to a high risk of exposing patients to other infections.

Currently, Haematopoietic (bone-marrow) transplantation is practised in the treatment of SCA [21]. Although it has proved successful in a number of cases, it is still not widely practiced due to the difficulties faced in finding an appropriate donor-match.

Table 1
Showing the timeline of events in the history of SCA.

Timeline	Events
1910	Sickle Cell Hemoglobin (HbS) detected in the blood stream by James Herrick.
1948	SCA identified in infants only after levels of fetal hemoglobin (HbF) dropped; thus initiating a theory that HbF showed a beneficial effect over the disease [13].
1957	The mutational basis (point mutation) underlying the disease was determined [12].
1980	Clinical trials undertaken with 33 SCA patients. Erythrocyte adherence to the endothelium was identified to be a key aspect contributing to the severity of the disease [18].
1998	FDA approves the use of Hydroxyurea (an inducer of HbF) for the treatment of adult SCA patients.
2000–2002	Studies on Ion-channel blockers that control cation homeostasis initiate in order to control increased permeability of erythrocytes, detected to initiate polymerization of HbS that eventually leads to sickling [16,17]. Research focuses on compounds regulating the expression of pro-adhesive molecules (aiding erythrocyte adherence to the endothelium) at the transcriptional level [19].
Present	Treatment with Hydrea, blood transfusion and haematopoietic transplantation/CBT is currently practiced in the treatment of SCA.

3. Existing therapies for the management of SCA

3.1. Hydroxyurea therapy

The use of Hydroxyurea or Hydrea in the treatment of SCA was approved by the Food and Drug Administration in 1988.

Multiple mechanisms of action have been attributed to the use of Hydrea; one such mechanism being the re-synthesis of HbF in adults. Under normal circumstances, a general shift from HbF to HbA/HbS (in the case of SCA patients) is observed within a few months after birth (6–12 months) [22]. Clinical symptoms of SCA are known to arise only after levels of HbF drop. This is usually because the increasing synthesis of HbF brings about a decrease in the overall levels of HbS [14].

Hydroxyurea is also known to function by causing a reduction in the number of white blood cells and also by acting as a nitric oxide donor in blood cells. Other mechanisms of function include a reduced expression of certain cell adhesion molecules that promote vaso-occlusive crisis.

One of the major underlying drawbacks of the use of Hydrea is its reported toxicity in a number of cases. It was observed that an increased dosage brought about an increased therapeutic effect, however greater was the subsequent toxicity [23]. Further, being a cell-cycle specific agent, long-term adverse effects were also speculated upon the prolonged usage of the drug [15].

A particular randomized controlled trial was carried out for nearly 18 years to assess the benefits versus risks of Hydrea treatment among adults [24]. According to this study, treatment initiated after 40 years of age proved to be associated with lower risks, while also showing a considerable reduction in morbidity.

Since Hydrea has been known to be cytotoxic, its use was approved only for adult patients. Early evidences supporting the use of the drug for the treatment of children were inadequate. Clinical trials and subsequent follow-up analysis did not provide satisfactory results to support its use among children.