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Editorial Open Access

Sickle Cell Disease: New Pharmacological Approaches

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Abbreviations: SCD: Sickle Cell Disease; Hb: Hemoglobin; RBC: Red Blood Cell; HU: Hydroxyurea; FDA: U.S. Food and Drug Administration; NO: Nitric Oxide; HbF: Fetal hemoglobin; TNFα: Tumor Necrosis Factor alpha

Editorial

Sickle cell disease (SCD) is a hematological disease characterized by punctual mutation of βGlu6 in Hb to βVal6 in HbS. The polymers formed in deoxygenated state change the red blood cell (RBC) cytoskeleton forcing them to adopt rigid, sickle like shapes [1]. In addition, an inflammatory process installs increasing pro-inflammatory cytokines and adhesion molecules that allow interaction between RBC, leukocytes and vascular endothelium [2]. All these factors together promote the vaso-occlusion – main phenomenon of SCD and responsible for clinical complications such as painful crisis, strokes, pulmonary hypertension, priapism, acute chest syndrome among others [3].

Nowadays, hydroxyurea (HU) is the only drug approved by the U.S. Food and Drug Administration (FDA) to treat SCD. HU is commonly used to treat a variety of myeloproliferative disorders by inhibited the enzyme ribonucleotide reductase involved in DNA synthesis. After metabolism, HU is bioconverted to nitric oxide (NO) which is responsible for numerous HU benefits, including the induction of gamma globin gene expression, vasodilatation and the inhibition of platelet aggregation [4]. However, HU demonstrated genotoxic and mutagenic potential for long-term treatment [5,6]. Furthermore, some patients are not responsive to HU-treatment. So, the discovery of new approaches to treat SCD symptoms is an important aim to be achieved.

Among the new strategies to be used to discovery new compounds to treat SCD we can highlight: a) compounds that induce gamma globin gene expression and HbF synthesis; b) agents that increase NO bioavailability; c) chelating agents; d) agents that inhibit Gardos channel, preventing hemoglobin dehydration; e) compounds that bind covalently to HbS, inhibiting the polymerization process and; f) compounds that modify rheological blood properties such as polaxamer 188 [7].

Despite the efforts to discovery new compounds few advances have been reached. We have proposed that hybrid compounds which combine multiple activities in the same molecule are an interesting strategy to discovery new drug candidates to treat SCD symptoms [4]. It has been shown that thalidomide and some derivatives (pomalidomide and lenalidomide) are able to induce gamma-globin gene expression and HbF synthesis [8,9]. So, we have proposed that thalidomide derivatives containing a nitric oxide donor subunit could be an alternative to HU [10]. The compounds demonstrated ability to induce gamma-globin expression and HbF synthesis. In addition, they demonstrated an important anti-inflammatory profile reducing the levels of pro-inflammatory cytokines such as TNFα [10,11]. In order to investigate the relationship between nitric oxide levels and the ability to induce gamma-globin gene expression we have obtained compounds with different levels of nitric oxide donation using furoxan as NO-donor subunit. However, despite all compounds demonstrated different analgesic activity profile we have no observed difference in gamma-globin gene expression (unpublished results). These results have demonstrated that combining the properties of thalidomide derivatives with NO-donor ability is a new successful approach to discovery compounds which could be a therapeutic alternative to HU in SCD treatment.

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