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European Network for Rare and Congenital Anaemias

Executive Agency for Health and Consumers

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Erythrocyte acting Therapies of Hemoglobin Disorders

The most important factors in the pathophysiology of severe β thalassemia are the excess of "free" and unstable α globin and α hemoglobin chains, heme derivatives and iron toxicity being responsible for increased hemolysis and ineffective erythropoiesis. The relative excess of α chains is initiated by the imbalance ratio between α and β + γ globin chains and the rate of protein synthesis. The clinical benefit and reduction of unpaired α hemoglobin chains is well demonstrated in β-thalassemic patients upon additional α thalassemic determinants or heterocellular forms of the hereditary persistence of fetal hemoglobin. Other factors are less explored, such as the inadequate capability of erythroid cells to prevent the instability of the soluble α chains and to improve proteolysis, upon the ubiquitin/proteasome system or using other proteases. The proteolytic process is efficient enough to remove the excess of unpaired α chains in erythroid cells of β-thalassemic trait carriers, but it is oversaturated upon additional α gene triplication, dominant mutation and in E/β-thal.compound heterozygotes.
The group of Yelena Ginzburg (Huihui Li et al., Nature Medicine, 2010) demonstrates the benefit of slowing down the iron loading in erythroid cells in mouse β-thalassemia, by using daily injections of human transferrin. The amount of precipitated α hemoglobin is highly decreased as well as hemolysis. The erythrocyte survival and the hemoglobin level in blood are well improved. This encouraging proof of concept indicates that inhibitors of erythroid transferrin receptors may be beneficial. Other agents, such as the intracellular iron scavengers and antioxidants could be also effective, alone or in combination.

Sickle cell anemia is a mixt to various extents of two different syndromes: the "hyperhemolytic vasculopathy" and the "vaso-occlusive events". The primum movens for both syndromes is the formation of polymers of hemoglobin S in erythrocytes, highly dependant upon the hemoglobin S concentration in erythrocytes and deoxygenation. The mechanism of intravascukar hemolysis in sickle cell anemia is poorly understood. However, it is known that inhibitors of the Gardos channel (calcium dependant potassium channel K_{ca} 3.1), like clotrimazole and the derivative Senicapoc (ICA-17043-05) and magnesium pidolate which inhibits the erythrocyte K^+Cl^- co-transport system are preventing or reverting dehydration of sickle cells and reduce hemolysis, both in sickle mice and in patients. Up to now, the clinical benefits were not adequately evaluated in a phase II study of Senicapoc (KI Ataga et al. Blood 2008), because the increase in hemoglobin improved the hyperhemolytic syndrome but the frequency of the painful crisis was maintained or even increased in patients in some patients. An ongoing phase III trial of Senicapoc has to take separately these two syndromes into

consideration. In addition, it will be useful to evaluate the inhibitors of Ca^{2+} permeable cation conductance, active specifically upon deoxygenation and stretching of sickle red blood cells. It is inhibited by carbone monoxide 25 ppm pretreatment, dipyridamole, DIDS and mechanotoxine-4 (DH Vandorpe et al. Plos one 2010). The combination of these approaches and with the hydroxycarbamide therapy could be beneficial.