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Editorial

World Sickle Cell Day 2022: Progress & prospects

World Sickle Cell Day, an annual event held on June 19, was established by a resolution of the United Nations in 2008, almost a century after sickle cell disease was introduced to the Western world by James Herrick's description of 'peculiar elongated and sickle-shaped red blood corpuscles' in the blood of an anaemic West Indian student[1]. A discussion in 1945 with William Castle, a haematologist interested in sickle cell disease, led Linus Pauling to hypothesize that this disease was a disorder of haemoglobin. Pauling's laboratory subsequently identified a variant haemoglobin in sickle cell anaemia, heralding the inception of molecular medicine[2,3].

Easy access to haemoglobin, globin mRNA and genomic DNA from erythrocytes, reticulocytes and leucocytes allowed sickle cell disease (and thalassaemia) to be the first human diseases whose aetiology and pathophysiology were characterized at a molecular level. A point mutation (p.glu7val, G*A*G→G*T*G) in the β-globin (*HBB*) gene codes for the synthesis of sickle haemoglobin (HbS; $\alpha_2\beta^S{}_2$). This variant, the first abnormal haemoglobin described, polymerizes when deoxygenated, damaging erythrocytes and triggering a complex pathophysiology culminating in sickle vaso-occlusion and haemolytic anaemia. Vaso-occlusion is associated with intermittent acute painful episodes and the pneumonia-like acute chest syndrome; chronic intravascular haemolysis causes decreased nitric oxide bioavailability, resulting in the late-developing vascular complications of pulmonary hypertension and nephropathy[4]. Foetal haemoglobin (HbF; $\alpha_2\gamma_2$), encoded by the γ-globin genes (*HBG2* and *HBG1*), is the predominant haemoglobin from early gestation to just before birth. HbF exerts a powerful anti-polymerization effect because it and its hybrid tetramer ($\alpha_2\gamma\beta^S$) are excluded from the HbS polymer[5]. By preventing HbS polymerization HbF affects the primary pathophysiologic event of this disease, although with differential magnitudes of effect on the acute and chronic complications. Most adults of African descent with sickle cell anaemia have about five per cent HbF; when the HbS gene is present with the Arab-Indian *HBB* haplotype, for reasons still incompletely understood adults have about 16 per cent HbF. The relationship between HbF level and the severity of sickle cell disease is complicated. Per cent HbF or g/dl of HbF in blood cannot predict the clinical course for an individual because HbF is restricted to a subset of erythrocytes called F-cells, and within a population the distribution of concentrations of HbF among F-cells is heterogeneous. Each erythrocyte contains approximately 30 pg of haemoglobin. HbS polymerization is nearly totally prevented when the sickle erythrocyte contains about 10 pg of HbF, although lower concentrations are also beneficial. If nearly all sickle erythrocytes contain about 10 pg of HbF, the phenotype of sickle cell anaemia is abolished[5-7]. The relatively poor safeguard HbF affords from the vasculopathic complications of disease might be a function of insufficiently high concentrations of HbF in some cells allowing their intravascular haemolysis and nitric oxide depletion[4]. Mechanisms accounting for the switch from foetal to adult erythrocytes haemoglobin synthesis are partly understood and are governed in large part by the activation of HbF repressors like the gene *BCL11A*. Reversing the haemoglobin switch has the capacity to 'cure' sickle cell disease if enough HbF or HbF-like haemoglobin can be induced in most erythrocytes[8,9].

From 1910 to 1998, a pharmacologic treatment directed to the molecular basis of sickle cell anaemia was not available. Analgesics for pain, transfusion for anaemia, antibiotics for infection and fluid replacement were the cornerstones of management. In 1998,

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hydroxyurea (hydroxycarbamide) was introduced[10]. This drug induced increased levels of HbF reducing both sickle vaso-occlusion and haemolysis along with morbidity and mortality. In 2019, two other drugs, voxelotor and crizanlizumab, were approved by the US Food and Drug Administration (FDA)[11,12]. Voxelotor increases haemoglobin-O2 affinity, thereby decreasing the polymerization of deoxyHbS, reducing haemolysis and increasing haemoglobin concentration. An effect on acute vaso-occlusive complications, although likely, has not been shown definitively. Crizanlizumab inhibits sickle cell-endothelial interaction by blocking P-selectin, preventing the early steps of sickle cell-endothelial cell adhesion and vaso-occlusion; it has no effect on haemolytic anaemia. In the current treatment paradigm, hydroxyurea, is the standard of care for nearly all patients; regardless of symptoms should be started in early infancy at maximally tolerated doses[13]. When used in this manner, children usually have outstanding responses. HbF levels can exceed 40 per cent with total haemoglobin concentrations beyond 11 g/dl, while vaso-occlusive episodes and side effects are uncommon. Beyond childhood, initiation of hydroxyurea is associated with more varied clinical and laboratory responses. While most properly dosed patients will have some benefit, it is almost never enough as acute vaso-occlusive events and haemolytic anaemia continue. This suggests that either voxelotor, crizanlizumab or both should be added to hydroxyurea in a combination treatment regimen. How these drugs might be sequenced is unsettled requiring further study[14]. Long-term follow up is also required to see if the superior effects of hydroxyurea started in very early life will persist. If they do, and if long-term exposure to hydroxyurea beginning in infancy is safe, one can envision major changes in disease management from adolescence onwards, a reduced imperative for combination chemotherapy and perhaps even cell-based therapeutics with curative intent.

Current drug therapy, especially in adults, helps most but cures none. Potentially, curative treatments with cell-based therapeutics are evolving rapidly, led by the outstanding results of allogeneic haematopoietic stem and progenitor cell (HPSC) transplants from matched sibling donors. Unfortunately, <20 per cent of patients have such a donor[15]. Gene therapy using autologous HPSCs that are altered *in vitro*, extends the possibility of curative cell-based therapeutics to all patients with the additional benefit of not requiring immunosuppression. Consonant with their early 'firsts', disorders of haemoglobin are again among the first to be treated with gene therapy including the first use of *CRISPR/Cas9* gene editing in patient stem cells. Early results appear to result in cure or near cure of both sickle cell anaemia and β thalassaemia[16-18].

Gene therapy entails: (*i*) drug-induced mobilization of bone marrow HPSCs; (*ii*) collecting these cells by apheresis; (*iii*) isolating the $CD34^+$ cells from the collected cells; (*iv*) altering the genome of these $CD34^+$ HPSCs; (*v*) chemotherapeutic ablation of patient bone marrow; (*vi*) reinfusing the altered HPSCs and waiting for their engraftment. Different gene-based therapeutic approaches are being explored using HPSCs and the following three are the most advanced; (*i*) adding to $CD34^+$ cells a 'HbF-like' modified HbA gene (HBB^{T87Q}) that prevents HbS polymerization and mimics HbF; (*ii*) using *CRISPR/Cas9* genome editing to disrupt an enhancer of *BCL11A* and downregulate *BCL11A* expression; (*iii*) using RNA interference to reduce the expression of *BCL11A* and increase HbF-gene expression[4]. These approaches have resulted in levels of HbF or anti-sickling HbA of about 40 per cent of total haemoglobin while reversing totally or nearly totally the phenotype of sickle cell disease[4]. Another target of gene therapy is the direct correction of the HbS mutation using homology-directed repair. HbS gene correction could be a superior approach to sickle cell disease as it does not require pancellular distribution of HbF or raise issues of O_2 transport because of the high O_2 affinity of HbF. Expression of the repaired gene must be sufficiently robust to result in balanced globin synthesis without causing a thalassaemia phenotype. Trials of this approach have just started[19]. Other targets and methods of gene therapy are being vigorously pursued, including the *HBG* promoters and base editing. It is too early to know which will turn out to be the best. The safety profile for gene therapies that require stem-cell mobilization and collection and myeloablative conditioning mirrors that of allogeneic HPSC transplantation. Gene therapy is still in its very early days so the excellent results should not be oversold. Among the many unknowns are possible off-target adverse effects of genomic editing, whether cellular therapeutics, especially those using lentiviral vectors, increases the risk of myeloid malignancy and if the early results of HbF induction are lifelong[20]. To be widely adopted, any therapy whose preparatory

stages are arduous, whose costs will be concerning and whose risks might not be known for years, should have enormous benefit.

What progress might we expect in the coming decades? Sickle cell disease is global, disproportionally affecting the disadvantaged. Curing a few patients at a well-resourced academic medical centre is not an effective treatment for the population at risk. Lacking an inexpensive pill that magically induces very high pancellular levels of HbF, or a simple in vivo gene editing programme not requiring HPSC mobilization or myeloablative conditioning, the prospects for an effective 'cure' in the near and medium-term seems remote. Neither combination drug therapy, which could cost tens of thousands per year for a lifetime nor cell-based therapy that is expected to cost $1 to $2 million are practical therapeutic solutions where sickle cell disease is most prevalent[21]. Hydroxyurea monotherapy was safe, beneficial and life-saving in Africa when given under the aegis of a clinical trial where compliance and follow up were closely monitored[22]. Whether fixed dose or titration to maximally effective dose hydroxyurea is similarly beneficial absent the free medicine and external support of a clinical trial, or if the results of the African study can be replicated is unknown. Nonetheless, screening, counselling, access to basic preventive health care, along with hydroxyurea for all should reduce morbidity and mortality where it might take decades for more sophisticated management options to arrive.

***Conflicts of Interest*:** None.

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