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INTRODUCTION

Recent advances and treatment challenges in patients with non-transfusion-dependent thalassemia

The thalassemias represent a diverse group of inherited hemoglobin disorders resulting from defective synthesis of either the alpha (α)- or beta (β)-globin chains, leading to an imbalance in α- or β-globin chains and ineffective erythropoiesis. Although many patients with thalassemia, including α- and β-thalassemia major, are severely anemic and require life-long transfusion therapy for survival, a subset of patients demonstrate less severe anemia and only require occasional blood transfusions. These disorders are classified as non-transfusion-dependent thalassemias (NTDTs) and will be the focus of this supplement.

Inherited hemoglobin-related disorders such as thalassemias are particularly common in areas of the world such as sub-Saharan Africa, the Mediterranean, and Southeast Asia, although continued migration worldwide has greatly expanded the reach of these diseases into large, multiethnic western cities. Studies continue to elucidate the underlying epidemiologic distribution of thalassemia, which must be considered when designing and implementing effective screening programs worldwide. The high prevalence of hemoglobin mutations in particular parts of the world often leads to simultaneous inheritance of 2 different thalassemia mutations from each parent or co-inheritance of thalassemia with structural hemoglobin variants, such as hemoglobin E. This results in a wide spectrum of disorders with varying severity and complicates diagnosis and treatment decision-making. In addition, the clinical phenotypes of individual NTDTs vary widely, influenced by multiple factors such as the amount of hemoglobin synthesized, the number and type of mutations in the globin gene, and other genetic modifiers. Although our understanding of NTDT biology continues to increase, a number of important questions remain concerning the regulation of α- and β-globin genes and the mechanisms behind such diverse phenotypic variations. In the first 2 articles of this supplement, Professor Sir David Weatherall and Professor Renzo Galanello, respectively, highlight current perspectives and recent advances in the epidemiology and molecular understanding of NTDT.

Non-transfusion-dependent thalassemia is associated with a number of physiological consequences, including ineffective erythropoiesis, iron overload, and hypercoagulability. The incidence and severity of clinical consequences attributed to these mechanisms differs from those with β-thalassemia major and are influenced by several factors, including the type of NTDT inherited, subsequent treatment of the disease, and inherent patient characteristics. The mechanisms underlying these clinical events are complex and often intertwined, although recent preclinical and clinical investigations continue to reveal the pathophysiology and specific signaling pathways involved. These discoveries allow improved understanding of how to prevent, monitor, and manage these consequences, and in some cases present an opportunity to develop novel therapeutic agents to improve patient outcomes. In the third article, Dr. Stefano Rivella examines the role of ineffective erythropoiesis in NTDT and novel investigational strategies for restoring normal erythropoiesis and iron metabolism. The fourth article, written in collaboration with Dr. John Wood, and the fifth article in collaboration with Dr. Erika Poggiali, highlights the pathophysiology and clinical impact of iron overload and hypercoagulability, respectively, as well as strategies for preventing and monitoring the resulting complications.

Management strategies for the primary forms of NTDT, including β-thalassemia intermedia (TI), hemoglobin E β-thalassemia, and α-thalassemia intermedia (also known as hemoglobin H disease), vary greatly depending on the clinical complications experienced by individual patients. Although all 2 disorders are considered non-transfusion-dependent, transfusion therapy may still play a role in treatment, along with iron chelation therapy. β-Thalassemia intermedia is associated with potentially long-term severe complications involving the skeletal system, extramedullary hematopoietic tumor formation, thromboembolic and cerebrovascular events, and iron-related end-organ damage. Hemoglobin E β-thalassemia demonstrates clinical presentations ranging from mild asymptomatic anemia to increasing requirement for transfusion therapy. In patients with hemoglobin E β-thalassemia this is influenced by genetic modifiers and adaptation to anemia, both of which complicate treatment decisions. Phenotypic heterogeneity is also observed with hemoglobin H disease and is greatly influenced by the genotypic diversity of inherited mutations. In all cases, careful consideration should be given to patient and disease characteristics in order to optimize treatment strategies and prevent unnecessary long-term transfusion therapy. In the sixth article, written in collaboration with Professor Mehran Karimi, we will discuss treatment strategies for patients with TI. Professor Nancy Olivieri and Dr. Elliott Vichinsky address management of hemoglobin E β-thalassemia and hemoglobin H disease, respectively, in articles 7 and 8. These articles provide an assessment of current management strategies, areas of recent progress, and questions for further investigation.

This supplement concludes with an article by Professor Swee Lay Thein focused on the emerging role of fetal hemoglobin (HbF) induction in patients with thalassemia. High expression of HbF has been shown to reduce anemia and transfusion dependency in patients with β-thalassemia. Improved understanding of the regulation of HbF expression naturally led to investigation of HbF-inducing agents for the management of β-thalassemia, with several agents demonstrating efficacy. This article discusses the current status of HbF induction therapy in patients with thalassemia, challenges in the development of such agents, and the potential role of this strategy in those specifically diagnosed with forms of NTDT.

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In recent years, researchers and clinicians have made substantial strides in overcoming challenges of inherited hemoglobin-related disorders. Greater understanding of the epidemiology and pathophysiology of these diseases continues to inform and improve strategies for screening, diagnosis, prevention, and management. Emerging novel agents and therapeutic strategies seek to improve patient outcomes, and recent advances continue to translate into longer survival for patients with NTDT. In turn, the expanded lifespan of patients with NTDT reveals serious, long-term complications that must be carefully monitored and addressed to positively impact quality of life. Continued collaboration and education are needed to ensure new measures to improve patient care are implemented in developing areas of the world. Despite recent advances, NTDT still represents a significant clinical challenge, and much work remains to be done to ensure a brighter future for the thousands of children affected by these disorders around the world.

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