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Original Article

Development of a new disease severity scoring system for patients with non-transfusion-dependent thalassemia

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ABSTRACT

Background: Patients with non-transfusion-dependent thalassemia (NTDT) present with a spectrum of disease severities. Since there are multiple pathophysiologies in such patients, tailoring treatment remains essential. Therefore, one simple, reliable tool would be beneficial to assess disease severity and tailor therapy, particularly for internal medicine specialists who may treat a variety of NTDT patients with a multitude of complications. This would allow for standardization of assessments leading to timely interventions and prevention of complications.
Methods: A working group of NTDT experts was formed to develop a new disease severity scoring system for adult and pediatric patients with NTDT, based on parameters considered to be most pertinent in defining disease severity.
Results: 20 parameters were selected for inclusion in the disease severity scoring system. An additional six parameters, largely related to growth and development, were selected specifically for pediatric patients (≤16 years of age). Consensus of expert opinion was used to establish the selected methods of assessment for each parameter, based on feasibility and availability of technology, cost containment, and avoidance of patient risk.
Conclusion: We propose that this new disease severity scoring system for adult and pediatric NTDT patients could be developed into a practical tool for widespread clinical use.

1. Introduction

Thalassemias are a group of inherited hemoglobin disorders characterized by impaired erythropoiesis, anemia and hypoxia due to defective α- or β-globin chain synthesis [1–4]. There are a number of clinical phenotypes with marked differences in symptom severity and treatment requirements observed – from clinically asymptomatic thalassemia trait, to severe anemia and transfusion dependence in β-thalassemia major – as a result of varying degrees of dysfunction in globin chain production [1–4]. Falling between the phenotypes of thalassemia trait and β-thalassemia major, non-transfusion-dependent thalassemia (NTDT) patients do not require regular transfusions for survival, but may require transfusions during periods of stress such as infection, pregnancy or surgery [5–7]. The primary forms of NTDT include β-thalassemia intermedia, hemoglobin (Hb) E/β-thalassemia and HbH disease, which are predominant in low- and middle-income regions, including parts of Africa (β-thalassemia intermedia), Southeast Asia (HbE β-thalassemia and HbH disease), East India and Bangladesh (HbE β-thalassemia). However, as a result of population migration, an increasing prevalence of NTDT has been observed in more developed regions, such as the USA and Europe, and is therefore becoming a worldwide health problem [2,7,8].

Patients with NTDT present with a broad spectrum of severities often influenced by environmental and genetic modifiers, from mild clinical presentation to severe symptoms, such as retardation of growth and development, and skeletal deformities [2,4,9–16]. Considerable differences in the attitude of clinicians regarding when it is best to treat or when to observe these patients also exist. Morbidity in NTDT is directly linked to the severity of ineffective erythropoiesis and peripheral

Abbreviations: ALT, alanine aminotransferase; dw, dry weight; ELISA, enzyme-linked immunosorbent assay; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LIC, liver iron concentration; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; N/A, not available; MCID, minimum clinically important difference; NTDT, non-transfusion-dependent thalassemia; NYHA, New York Heart Association; PHT, pulmonary hypertension; QoL, quality of life; RNA, ribonucleic acid; SF, serum ferritin; TRV, tricuspid regurgitation jet velocity; ULN, upper limit of normal.

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hemolysis [17]. Expansion of the erythron as a result of ineffective erythropoiesis can lead to osteoporosis and bone deformities, hepatosplenomegaly and also extramedullary hematopoietic pseudotumors [15]. Abnormalities of platelets and pathological red blood cells can lead to a hypercoagulable state with increased thrombotic risk in patients with NTDT [18–20], as well as pulmonary hypertension [21,22], and leg ulcers [23,24]. Secondary to ineffective erythropoiesis, excess body iron accumulates as a result of increased gastrointestinal iron absorption alongside occasional blood transfusions, which also has a major etiological role in many complications [14–16,24–26]. Furthermore, with the progressive accumulation of iron over time, complications increase with advancing age [23], thus highlighting the importance of effective patient monitoring and early treatment intervention.

With this multiplicity of pathophysiologies and associated complications, one tool to evaluate patients on an individual basis is needed, with a view to initiating timely interventions that would prevent any further complications. A simple and reliable method of assessing disease severity would be useful in guiding management decisions in clinical practice, as summarized in Fig. 1. This would be particularly useful for internal medicine specialists who may treat a variety of NTDT patients with a multitude of complications.

A disease severity scoring system expresses an integrated assessment of the burden of disease in a given patient using a defined data set to comprehensively score the patient. Groups of domains populated with non-redundant items to be included within the scoring system need to be valid and reliable. Each item also needs to be easily captured using feasible, standardized methods of assessment, and weighted based on clinical relevance, including associated morbidity and mortality. Disease severity scoring systems have been developed and implemented successfully for a number of chronic diseases, including type I Gaucher disease and rheumatoid arthritis [27–30]. Other systems for grading the severity of NTDT have been proposed [31,32]; however, they were designed for use in patients with β-thalassemia intermedia or β-thalassemia/HbE disease only and were based on a limited number of parameters. Furthermore, some clinical criteria were based on the treating physician's judgment (i.e., age at first blood transfusion and requirement for regular blood transfusion), making it impractical to use when physicians employ different transfusion regimens. An accurate and comprehensive disease severity scoring system is yet to be developed and validated for patients with NTDT for widespread use in routine clinical practice. Therefore, a working group of NTDT experts was formed to develop a new disease severity scoring system for adult and pediatric patients with NTDT. Once validated, we intend this to be developed into a practical tool for widespread clinical application. Here, we describe the methodology employed in generating this new NTDT disease severity scoring system. Details regarding the testing of the instrument for validity, reliability and feasibility will be published separately.

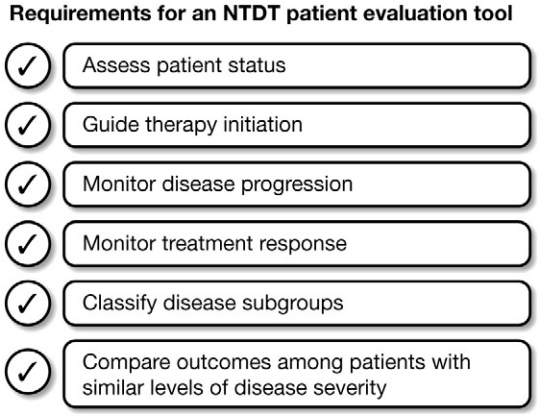

Fig. 1. Summary of the requirements for a tool to evaluate patients with NTDT.

2. Methods

2.1. Instrument development and selection of domains

A Disease Severity Scoring System working group comprising eight global NTDT experts, was formed (M. Domenica Cappellini, Ali T. Taher, Antonis Kattamis, Vip Viprakasit, John B. Porter, Khaled M. Musallam, Renzo Galanello and David J. Weatherall). The novel scoring system was constructed based on parameters thought to be most pertinent by these experts in defining disease severity in NTDT patients, based on their clinical experience and expertise. The impact of each parameter on disease severity and appropriate thresholds was decided upon either according to published literature or the expertise of the group, based on an association with worse outcomes. Parameters were then assigned a severity weighting according to the extent that morbidity and mortality in that parameter contributes to disease severity in NTDT patients. Temporal aspects of each parameter were also considered; for example, which are important at (or near) the time of assessment, and which are important over the course of the disease, irrespective of when they occurred. As such, parameters may indicate a more severe status if defined as 'currently active'.

The disease severity scoring system was thus developed based on group consensus comprising general parameters for all patients (adult and pediatric patients; Table 1A), with additional parameters specifically for pediatric patients only (Table 1B).

3. Results

In total, 20 parameters were finally selected by the Working Group for inclusion in the disease severity scoring system for the screening of NTDT patients (Table 1A). An additional six parameters, largely related to growth and development, were selected specifically for pediatric patients (≤16 years of age; Table 1B). Each parameter contains two or more items that would be scored individually by the evaluating physician. The domain score would then be tabulated by summing the score for all parameters. The total score would be the sum of the domain scores, with a maximum of 52 points for adult patients and 62 points (52 + additional 10) for pediatric patients.

Consensus of expert opinion was also used to establish the selected methods of assessment for each parameter, based on feasibility and availability of technology, cost containment, and avoidance of patient risk. Thus, tools that are uniformly available, practical in terms of standard of care, and for which there is a near consensus of global standardization were selected. Patient quality of life (QoL) in particular was considered too challenging to standardize. The Working Group suggested that evaluation is usually conducted outside of standard care and therefore this domain was not included in the scoring system but may be used later for validation. Similarly, investigational parameters, such as non-transferrin-bound iron and hepcidin, were not included as they are not yet well established and methodology is not routinely available. Furthermore, factors introduced as part of physician intervention (e.g., splenectomy, transfusion, iron chelation, fetal hemoglobin induction and other methods of treatment for specific complications) were excluded from the system as the score was designed to capture only the natural history of disease; assessing its dynamic changes upon external interventions would occur in later stages of validation and development.

4. Discussion

As a result of the clinical heterogeneity and progressive accumulation of complications in patients with NTDT, the management of patients cannot be simply generalized. Patients with NTDT need to be