Complications of β-thalassemia major in North America

Melody J. Cunningham, Eric A. Macklin, Ellis J. Neufeld, and Alan R. Cohen, for the Thalassemia Clinical Research Network

Treatment of patients with β-thalassemia major has improved dramatically during the past 40 years; however, the current clinical status of these patients remains poorly characterized. We performed a cross-sectional study of 342 patients in the Registry of the National Institutes of Health-sponsored Thalassemia Clinical Research Network. Evidence of hepatitis C exposure was present in 35% of tested patients, was associated with age, and had a rate of spontaneous viral clearance of 33%. Ferritin levels ranged from 147 to 11 010 ng/mL (median, 1696 ng/mL). Median hepatic iron content was 7.8 mg/g dry weight and 23% of patients had values of 15 mg/g dry weight or higher. No patients 15 years or younger and 5% of patients aged 16 to 24 years had heart disease requiring medication. Ten percent had cirrhosis on biopsy. Endocrinologic complications were common among adults. Seventy-four (22%) patients had recent implantable central venous access devices (CVADs) placed. Among 80 episodes of bacteremia in 38 patients, 90% were attributable to the CVAD. Among 330 patients who had received deferoxamine chelation therapy, 224 (68%) reported no complications. We conclude that hepatitis C, iron-related organ dysfunction, and complications of iron chelation therapy are strongly age-dependent in North American patients with β-thalassemia. (Blood. 2004;104:34-39)

Introduction

To assess the current clinical status of North American patients with transfusion-dependent thalassemia major, to define the complications that appear in this group of complex patients, and to lay the groundwork for future clinical trials, the Thalassemia Clinical Research Network (TCRN) of the National Heart, Lung and Blood Institute (NHLBI) created a registry. This includes relevant data on more than 700 patients, 342 of whom have severe transfusion-dependent β-thalassemia. This is the largest group of North American patients with this disease ever assembled. Among transfusion-dependent patients with β-thalassemia, a wide spectrum of complications arise from obligatory lifelong transfusions of packed red blood cells. These include blood-borne infections, iron overload, toxicities of iron chelation, and bacterial infections. Although the clinical management of thalassemia has changed dramatically, the results of these changes, as reflected in the current clinical status of patients in North America, are poorly characterized. In the current study we report on the largest cohort of North American patients to date.

Patients and methods

The TCRN is a clinical research network, funded by the National Institutes of Health, composed of 5 core centers in North America, 13 clinical satellites, and a data-coordinating center (Appendix 1). The TCRN developed a registry to characterize demographic and clinical features of North American patients with thalassemia, to highlight areas requiring clinical research, and to identify candidates eligible for clinical research protocols. Only living patients were enrolled into the TCRN registry. Analysis of the registry data provides a cross-sectional view of the current state of thalassemia in North America. Registry data were assembled by retrospective chart review and in some instances by patient self-report (eg, when events occurred at other institutions) using a case report form with 14 sections covering demographic, genetic, infectious, endocrine, cardiac, hepatic, iron-related, and deferoxamine (DFO)–related complications. Specific questions regarding complications are included in Appendix 2.

Current and retrospective data for this report were entered once for each subject during the time period from May 2000 through April 2003. Ages reported here are the ages at registry enrollment or at the time of particular events in the registry dataset. Institutional review boards approved the protocol at each site and each subject or a parent or guardian gave informed consent.

Genotype

The registry included α- and β-globin genotypes were available, and if so, documented the specific α and β alleles. In this retrospective review from more than 40 years of data, many different methods were used. A manuscript describing this is in preparation (E. Vichinsky, E.A.M., N. Olivieri).

Definitions

For the purposes of this report, β-thalassemia major (TM) was defined as homozygous (or compound heterozygous) β-thalassemia requiring 8 or more transfusions in the 12 months prior to enrolling in the registry. Patients with hemoglobin E/β-thalassemia and nontransfused thalassemia variants were excluded from this analysis, as were patients with successful engraftment of transplanted stem cells. By the TCRN definition, patients with β-thalassemia who required fewer than 8 transfusions annually are
considered to have thalassemia intermedia and are not considered in the present analysis. This included several patients who might otherwise have been considered TM but had suspended regular transfusions prior to enrolling in the registry (eg, due to transfusion reactions or use of alternative therapies).

Data validation

More than 80% of all registry forms have been partially reviewed with sites, targeting data of specific interest, including diagnoses, genotyping, endocrinopathies, hepatitis C testing, ferritin concentrations, and biopsy results. One hundred percent of the positive diabetes data were validated. Independent source document verification was conducted for selected variables on approximately 20% of registry forms.

Statistical methods

Age trends in incidence rates were tested by Cochran-Armitage trend tests. Associations of categorical variables were tested by the Fisher exact test. Differences of medians for continuous measures were tested by exact Wilcoxon-Mann-Whitney rank sum tests. Locally weighted regressions of proportions of patients with elevated iron stores were fit using generalized additive models for binomial data with a logit link function (S-Plus 6.1).

Results

The registry included 342 patients with TM; 74% of patients reported β-globin genotyping. The 5 most common genotypes, reflecting combinations of 3 common haplotypes, are shown in Table 1.

Transfusion-transmitted infections

Of 334 patients tested for hepatitis C virus (HCV), 35% were seropositive or positive for HCV RNA. Laboratory evidence of HCV exposure was significantly associated with age (Table 2), occurring in 5% of patients younger than 16 years, 23% of patients 16 through 24 years old, and 70% of patients 25 years or older (P < .001 by Cochran-Armitage trend test). Among patients tested for both HCV antibody (Ab) and RNA, 26 of 75 seropositive patients (35%) were subsequently HCV RNA negative. This includes 20 of 61 patients (33%) with no report of treatment who apparently cleared virus spontaneously. Three of 9 (33%) treated with interferon monotherapy and 3 of 5 (60%) treated with interferon and ribavirin had cleared virus. Eight of 311 (2.5%) patients tested for hepatitis B surface antigen had positive results. Two percent of TM patients in the registry were positive for HIV.

Iron overload

Hepatic iron content (HIC), assessed by biopsy (93%) or magnetic susceptibility (7%), and serum ferritin levels were tested within 2 years of registry entry in 166 and 330 patients, respectively. Median serum ferritin level was 1710 ng/mL (range, 147-11 010 ng/mL; Figure 1A). Median HIC was 7.8 mg/g dry weight (range, 0.9-43 mg/g dry weight; Figure 1B). Twenty-three percent of the patients had HIC equal to or greater than 15 mg/g dry weight (ages 2-39 years), a level at which more aggressive chelation has been recommended because of increased risk of morbidity and mortality.2,5 Of 35 patients with a report of heart disease, 15 have HIC

### Table 1. Genotypes for β-thalassemia major patients (of 254 with β-globin genotyping)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codon 39 (C&gt;T)</td>
<td>29 (11.4)</td>
</tr>
<tr>
<td>IVS-1-110 (G&gt;A)</td>
<td>26 (10.2)</td>
</tr>
<tr>
<td>Codon 39 (C&gt;T) codon 39 (C&gt;T)</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>Codon 39 (C&gt;T) IVS-1-110 (T&gt;C)</td>
<td>12 (4.7)</td>
</tr>
<tr>
<td>IVS-1-6 (T&gt;C)</td>
<td>11 (4.3)</td>
</tr>
</tbody>
</table>

*These represent the 5 most common genotypes.

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In this cross-sectional methodology, not every patient is screened for every test. Evidence of hepatitis C by liver biopsy was not queried by the database. For the endocrine disorders, the numbers of patients in each age group overall were 120, 93, 129, and 342, respectively.

*These results are of the patients (n = 75) with a positive test for anti-HCV antibodies and a concurrent or subsequent HCV RNA assay.

†These results are of the patients (n = 61) with a positive test for anti-HCV antibodies and a concurrent or subsequent HCV RNA assay who have never been treated for hepatitis C.
Data within 2 years of registry entry. Two of these 15 patients have HIC equal to or more than 15 mg/g; the other 13 (87%) have HIC less than 15 mg/g. There is a suggestion of higher body iron stores in patients from 10 to 25 years of age and lower iron stores in older patients (Figure 2A-2B). Figure 3 documents the poor association of ferritin and HIC and total body iron previously reported.2,6 Organ dysfunction due to iron overload was common in young adults with TM (Table 2). Twenty-three percent of patients 25 years or older had heart disease requiring medication. No patients aged 15 years or younger and 5% of patients aged 16 to 24 years were reported to have heart disease requiring medications. Of 232 patients with pathology results from liver biopsy, 24 (10%) had cirrhosis. Of these, 11 (46%) did not report clinical findings of liver failure or cirrhosis. The prevalence of cirrhosis by biopsy increased significantly with age (Table 2; \( P < .03 \)). Three percent of patients aged 15 years or younger and 6% of patients aged 16 to 24 years had evidence of liver failure or cirrhosis. The range of ferritin and HIC values in this group of patients was 221 to 9456 ng/mL and 1.3 to 36.4 mg/g, respectively. However, these data do not necessarily correspond with the onset of the complication because this is a one-time data collection. Of 130 patients aged 25 years or older, 17% were receiving treatment for thyroid disease, 9% for parathyroid disease, and 21% for diabetes. Sixty-two percent had received hormone replacement therapy for hypogonadism. Endocrinopathies were approximately half as prevalent among patients aged 16 through 24 years as those older than 25 years. No endocrinopathies were reported in patients aged 15 years or younger. There was no influence of gender on prevalence of endocrinopathies. Eleven pregnancies occurred in 8 of 101 female TM patients aged 18 years or older (7.9%). Seven were carried successfully to term; 2 miscarriages and 2 terminations were reported. Twelve of 94 men aged 18 years or older (13%) were reported to have fathered pregnancies.

Complications of iron chelation therapy
Among 328 patients who had ever received chelation therapy with DFO, 105 (32%) reported complications requiring modification of the dose or route of administration of the chelator. Twenty percent of 309 patients using DFO at the time of enrollment in the registry reported current complications. Table 3 identifies specific complications associated with therapy with DFO and their frequencies. Complications of chelation therapy with DFO were more common in older patients (Table 4; \( P < .001 \) by Cochran-Armitage trend test). Sixty of 129 patients (47%) aged 25 years or older ever reported complications versus 16 of 106 (15%) of patients younger than 16 years.

Twenty patients reported stopping DFO, whereas 14 young patients had not initiated therapy. Of the 20 who reported stopping DFO, the median age was 26 years after a median of 15 years using DFO. Of these patients, 3 (15%) had heart disease when enrolled in the registry (versus 10% of DFO users, \( P = .46 \)); however, the temporal relationship between cessation of DFO use and the date of

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development of heart disease is not known. The single-time data collection precludes knowing with certainty whether the patients stopped DFO temporarily or permanently. By report, 10 patients stopped due to noncompliance, 1 due to possible toxicity, and 1 for an unknown reason. The other 8 patients discontinued for reasons more likely to be temporary: 1 pregnancy, 1 oncologic surgery, 2 decreased iron stores, and 4 participants in an oral chelator trial. Severe local reactions at infusion sites were associated with stopping DFO. Eight of 28 patients (29%) with past severe local reactions stopped DFO compared with 12 of 299 patients (4%) without significant local reactions (Table 3; *P* < .001 by Fisher exact test). Higher ferritin level within 2 years of enrollment (median, 3026 versus 1634 ng/mL; *P* < .001 by exact Wilcoxon-Mann-Whitney rank sum test), but not HIC, was associated with past history of local reactions (Table 4).

Implantable vascular access devices, used for transfusions or for intravenous DFO infusion,7,8 are common among the thalassemia population. Seventy-four (22%) had surgically placed central vascular access devices (CVADs) within 5 years of registry entry. Patients using CVADs within 5 years of enrollment were generally older than those not using CVADs (median age, 26 years versus 19 years; *P* = .02 by signed rank test). CVAD placement was significantly associated with history of local reactions (Table 3; *P* < .001 by Fisher exact test). Among 80 episodes of sepsis or bacteremia occurring in 38 patients, 90% were attributable to the CVAD. Among CVAD-associated infections, staphylococcal infections predominated, causing 75% of the infections. *Stenotrophomonas, Escherichia coli, Candida,* and *Enterococcus* each caused 3% to 4% of the infections. Forty-three percent of patients with a CVAD developed infections related to the device.

### Discussion

We have defined the current status of complications among 342 patients with TM in North America. Complications can be grouped as (1) transfusion-transmitted infections, (2) transfusional iron overload, (3) toxicities of iron chelation therapy, and (4) bacterial infections. Age is directly related to the prevalence of most of these complications. This paper is the first attempt to compile such data on North American patients. Several of the network sites and satellites are known to be among the largest providers in the United States and Canada. It is possible that the data for registry patients are biased by age or severity, but the magnitude and sign of any bias are unknown.

#### Transfusion-related infections

Hepatitis C and HIV are no longer major threats in the North American blood supply. However, transfusion-acquired HCV remains one of the most important problems among patients with thalassemia, largely due to transfusions given before 1990.10,11 The 33% rate of spontaneous clearance in our patient population is favorable compared to the 10% to 20% rate reported in the general literature.12-14 It is also higher than the rate of 25% in patients with hemophilia exposed to blood products,15 and is substantially higher than the 0% remission reported in hemophilia patients coinfected with HIV.15 This clearance is only surpassed by infants with vertically transmitted HCV who demonstrate the highest rate of spontaneous resolution at 75%.16 A multicenter trial to address the efficacy of current HCV therapy with interferon and ribavirin in this patient population has been initiated. Reports of malaria17 and West Nile virus18-21 in the US blood supply suggests that blood safety cannot be completely ensured and that despite sensitive and specific testing, transfusion-related infections are still a concern.

#### Iron overload

**Endocrinopathies.** Hypogonadism, hypothyroidism, diabetes mellitus, low bone mass, and hypoparathyroidism22-27 are still common in young adults with TM. Our data are consistent with the Italian cohort in which no diabetes was reported in the subgroup of patients at the age of 15 years, born between 1980 and 1984.27 Our overall diabetes rate of 10% is higher than their overall reported rate of 5.6% but less than the 20% reported in Brittenham and coworkers’ cohort of 59 patients, aged 7 to 31 years.28 An analysis of low bone mass in thalassemia syndromes using data from the registry will be reported elsewhere (M. Vogiatzi, E.A.M., E. Fung, P. Giardina, manuscript in preparation).

**Heart disease.** Cardiac failure and rhythm disturbances remain the main cause of death among young adults with TM.2,28,29 In our cohort, no patients aged 15 years or younger and 5% of patients aged 16 to 24 years had heart disease requiring medication. In an earlier cohort of 1146 patients born from 1960 through 1987, Borgna-Pignatti and her coworkers found the incidence of heart failure by 15 years of age to be 5% in patients born between 1970 and 1974 and 2% in those born between 1980 and 1984.27 Further, in a cohort of 97 patients born before 1976, 37% had heart disease as defined by need for inotropic or antiarrhythmic medications.28 This can be compared to the 23% rate in patients older than 25 years of age in the present cohort who were born before 1978.

HIC of more than 15 mg/g dry weight is considered to be a risk factor for heart disease. Available data support the use of more intensive iron chelation (ie, higher dose per day or chelation more days per week) for patients with values in excess of this level.2,28,29 Because the registry data are not longitudinal, neither changes in dose over time, nor the resulting effects on

### Table 3. Complications of DFO therapy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Experienced complication</th>
<th>Did not experience complication</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>High-frequency hearing loss, no. (%)</td>
<td>59 (18)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Vision/retinal, no. (%)</td>
<td>19 (6)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Allergy, no. (%)</td>
<td>6 (2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Other, no. (%)‡</td>
<td>33 (10)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Severe local reactions, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stopped DFO, no. (%)</td>
<td>28 (9)</td>
<td>299 (91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median ferritin, ng/mL</td>
<td>8 (2.9)</td>
<td>12 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median HIC, mg/g dry weight liver</td>
<td>9.8</td>
<td>7.8</td>
<td>.27</td>
</tr>
<tr>
<td>CVAD placement, no. (%)</td>
<td>16 (56)</td>
<td>57 (19)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

— indicates did not experience.

*The other category includes 6 patients in whom poor growth was attributed to DFO therapy, 4 with gastrointestinal symptoms, 3 with Yersinia infections, and 2 each with tinnitus, metaphyseal dysplasia, and renal complications (failure and calculus).

### Table 4. Association between age and DFO complications

<table>
<thead>
<tr>
<th>DFO complications</th>
<th>0-15 y, % (no.)</th>
<th>16-24 y, % (no.)</th>
<th>25 y and older, % (no.)</th>
<th>Overall, % (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever experienced</td>
<td>15 (110)</td>
<td>31 (93)</td>
<td>47 (129)</td>
<td>32 (328)</td>
</tr>
<tr>
<td>Currently experiencing</td>
<td>5 (105)</td>
<td>22 (89)</td>
<td>33 (114)</td>
<td>20 (308)</td>
</tr>
</tbody>
</table>
HIC or heart disease are available. The exact relationship between HIC and heart disease is not well understood. Some patients have heart failure and arrhythmias at an HIC substantially less than 15 mg/g dry weight. Conversely, some patients with HIC more than 15 mg/g dry weight do not have heart disease. Because the registry contains data from only one clinical time point, we cannot judge whether historical HIC values predicted risk of cardiac complications. However, the data from our study show that a single HIC determination less than 15 mg/g dry weight does not preclude the presence of significant iron-induced cardiac disease.

**Liver disease.** The registry findings in regard to liver iron may reflect secular trends in chelation compliance, but other possible contributing factors include survival bias (the patients with worst iron by age 30 may die and be lost to the dataset; the patients with best iron may preferentially survive) and presence of cirrhosis (less iron per gram of liver if more fibrosis/cirrhosis). In addition, because fewer than 50% of the patients have undergone a liver biopsy within 2 years of enrollment, this raises the possibility that only the most compliant patients have agreed to this procedure (or the very worst ones who are forced to by their physicians). Older patients might be more compliant with their chelation, or might have genetic resistance to iron loading, promoting survival.

Published liver cirrhosis data bound our results. In an Italian cohort of 86 children with TM aged 15 years or younger and undergoing biopsy between 1976 and 1981, cirrhosis was evident in 19%. Among 73 TM patients from Hong Kong aged 1.5 to 22.5 years (mean, 11.7 years) and undergoing biopsy from 1992 to 1999, none had evidence of cirrhosis and 30% had liver fibrosis.

**DFO complications**

The majority of patients receiving DFO had no complications despite the fact that patients must administer the chelator by infusion for decades and at cumulative doses of several kilograms. Sixty-eight percent of all patients and more than 50% of patients 25 years and older have not reported complications of DFO. DFO-related problems are more common in older patients. Although this may reflect the fact that younger recipients had less time to develop DFO complications, the alternative and more likely explanation is that clinicians over time have learned to adjust the dose of DFO to prevent dose-related toxicity. Despite the excellent overall tolerability of DFO, some patients have stopped the drug, and those with severe local reactions have poor compliance and are at high risk of iron-related toxicity.

Local reactions to subcutaneous DFO are common among patients with thalassemia and, as noted, are a risk factor for cessation of chelation therapy. Pain and erythema at injection sites do not appear to be allergic in nature.

**Implantable CVADs**

Our data demonstrate that implantable CVADs are a major cause of bacteremia and risk of sepsis in this patient population. CVADs are commonly placed in younger patients for reliable transfusion access and in older patients to allow 24-hour chelation for heart disease, or because of severe local reactions to DFO.

**Limitations and conclusions**

Some limitations are inherent in this retrospective dataset. First, the cross-sectional methodology across a wide age range establishes a survival bias. For example, patients who previously succumbed to infections or to iron-induced heart disease are not part of the registry and therefore are not included in this report. Second, age-related complications are confounded by advances in therapy and diagnostics. For example, very few young patients are infected with hepatitis C not only because they are young, but because of the advent of hepatitis C screening in 1990. Similarly, patients over age 35 precede the DFO treatment era, and it is possible that this contributes to their iron-related complications. Third, the cross-sectional methodology does not allow an evaluation of the clinical response to abnormal laboratory studies, particularly elevated hepatic iron concentration. For example, high liver iron concentrations usually prompt more intensive iron chelation therapy. Fourth, patient self-report (when data were not available at the network center) may be biased, but the direction and magnitude of this bias are indeterminable. Finally, not every patient underwent every study. Therefore, a potential for selection bias exists. This may be most problematic for liver biopsies. Ascertainment of serious cardiac or endocrine abnormalities is less likely to be complete. With these limitations in mind, the present data still demonstrate a high prevalence of complications, some improvement when compared to older cohorts in the DFO era, and the need for further improvement in the management of these complex patients.

Improvements over the last 15 years include blood screening for HCV, individualization of DFO dosing, and less aggressive hypertransfusion (pretransfusion hemoglobin level 9-11 g/dL rather than 10-12 g/dL). Treatment of this profound disorder has also greatly improved in other ways during the last 4 decades. In the 1960s, most neonates with this disorder were infrequently given transfusions and destined to develop severe deformities and growth retardation followed by the lethal consequences of iron overload. Their life expectancy was less than 20 years. Today, as consequences of improved red cell transfusion schedules and the safe and effective use of subcutaneous DFO, children with thalassemia avoid serious deformities and have an improved life expectancy. But compliance is a problem in any disease that requires lifelong treatment, and subcutaneous DFO delivered by pump is not an easy therapeutic program with which to comply. Furthermore, complications in addition to iron overload, such as blood-borne infections, may arise from obligatory lifelong transfusions of red blood cells. Differences between the current study and previous studies in regard to patient populations, definition of specific complications, and types of analyses make comparisons of outcomes inexact. However, the present data suggest that some age-related complications may now occur less frequently in younger patients with TM.

**Acknowledgments**

The authors thank Drs. Nancy Olivieri and David Nathan for critical comments on the manuscript.

**Appendix 1: Study group members**

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Registry data reported in this paper.
References

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