Iron Chelation Adherence to Deferoxamine and Deferasirox in Thalassemia

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The Thalassemia Clinical Research Network collected adherence information from 79 patients on deferoxamine and 186 on deferasirox from 2007 to 2009. Chelation adherence was defined as percent of doses administered in the last 4 weeks (patient report) out of those prescribed (chart review). Chelation history since 2002 was available for 97 patients currently on deferoxamine and 217 on deferasirox, with crude estimates of adherence from chart review. Self-reported adherence to both deferoxamine and deferasirox were quite high, with slightly higher adherence to the oral chelator (97 vs. 92%). Ninety percent of patients on deferasirox reported at least 90% adherence, compared with 75% of patients on deferoxamine. Adherence to both chelators was highest in children, followed by adolescents and older adults. Predictors of lower deferoxamine adherence were smoking in the past year, problems sticking themselves (adults only), problems wearing their pump, and fewer transfusions in the past year. Predictors of lower deferasirox adherence were bodily pain and depression. Switching chelators resulted in increased adherence, regardless of the direction of the switch, although switching from deferoxamine to deferasirox was far more common. As adherence to deferoxamine is higher than previously reported, it appears beneficial for patients to have a choice in chelators.

For decades, the standard iron chelation therapy in thalassemia was deferoxamine (Desferal®, DFO), a subcutaneous or intravenous infusion, typically 8–12 hr per day, 5–7 days per week, and associated with poor adherence in some patients. Adherence is essential to decrease the risk of complications and mortality due to iron overload in transfused thalassemia patients. In 2005, deferasirox (Exjade®, Novartis), an oral chelator, was approved for use by the U.S. Food and Drug Administration (FDA). Oral chelation was hypothesized to have positive effects on adherence. However, many patients on both types of chelators find adherence difficult due to the burden, pain, and unpleasantness of administration, and side effects encountered. One study found that patients felt more distressed from their treatment than from the disease itself [1]. A review of chelation adherence [2] found studies reporting adherence to deferoxamine ($N = 7$), deferiprone ($N = 6$), and comparisons of the two ($N = 5$), but no studies reporting adherence to deferasirox. Estimated mean adherence ranged from 59 to 78% for deferoxamine and 79 to 98% for deferiprone. Comparative studies suggested higher adherence with the oral chelator. A recent trial of deferoxamine + deferiprone combination therapy [3] found an average of 89.9% adherence to deferoxamine compared to 93.3% for deferiprone ($N = 11$). Another review of deferoxamine [4] found that non-adherence rates ranged from 9 to 66%, but definitions varied by study and "adherence was often not measured objectively." They found no consistent predictors of adherence across studies. Other studies of deferoxamine reported that nearly 50% [5] and 74% [6] had missed at least one infusion in the previous month.

Participants on deferoxamine and deferasirox in this study were of similar age and race, but patients on deferoxamine were more likely to be female and from Canada (Table I). Roughly 15% of patients on both chelators reported having problems remembering chelation at least sometimes (Table I). Many patients reported problems with side effects (38% for deferoxamine; 21% for deferasirox), sticking themselves (46%), and wearing their pump for so many hours (41%). However, most patients reported regularly feeling successful with chelation therapy (71% for deferoxamine; 78% for deferasirox). Adherence to deferasirox was slightly higher than to deferoxamine (97 vs. 92%; Table I). 90% of patients on deferasirox reported at least 90% adherence, compared to 75% of patients on deferoxamine. As all prior studies were conducted before the FDA approval of deferasirox in 2005, the higher adherence to deferoxamine in the current study may reflect the fact that many of these patients are now on deferoxamine by choice. In addition, those on deferoxamine by medical necessity may have greater motivation for adherence due to increased risk of complications. Of the eight patients on combination therapy, adherence to both chelators was equivalent: 94% of doses taken and seven (88%) with at least 90% adherence.

Adherence was highest in children, followed by adolescents and adults aged 35 and older, and lowest between 25 and 35 years of age (Fig. 1). High adherence in children is likely due to parental insistence. Lowest adherence from 25 to 35 years possibly reflects conflicting time demands with careers and families. Alternately, it may illustrate a feeling of infallibility, before maturation and adherence to therapy later in life. However, the possible increase in adherence after age 35 in this cross-sectional data may reflect early deaths of less adherent patients, skewing the population of live thalassemia patients. It should be noted that our age-related findings do not conflict with prior studies [1,7] that found decreased adherence with older age, as those studies only included participants up to 30 years of age.

Independent predictors of deferoxamine adherence were problems sticking themselves (adults only) and smoking in the past year (Table II). Adults who reported never having problems sticking themselves had 97% adherence (88% with adherence $\geq$90%) compared to 74% adherence among adults who reported often having problems (33% with adherence $\geq$90%). Adherence to deferoxamine was 80% in smokers compared to 94% in nonsmokers aged 10 and older, likely mirroring bad health-related choices in general. Smoking was not a significant independent predictor of adherence $\geq$90% or chelation $\geq$5 nights/week, but there was a trend towards decreased adherence in participants reporting problems wearing their pump (Table II), with 92% chelated at least 5 nights/week in participants who reported no problems compared to 66% in those who reported problems at least sometimes. Increased number of transfusions in the past year was also associated with chelation at least 5 nights/week, potentially revealing adherence to treatments all around, or acknowledgement of especially high risk of iron overload. Another factor significant in initial bivariate analysis was days per weeks that deferoxamine was prescribed, with a decrease in adherence with increased number of days. This may reflect increased difficulties in adherence to additional days, or alternatively, physicians prescribing additional days to less adherent patients.

Lower deferasirox adherence was associated with depression in adults and adolescents (Table II), likely at least in part caused by their depressed state. This suggests that screening and treatment for depression should be key components in thalassemia care. On the other hand, patients reporting more anxiety symptoms had a trend towards higher adherence, possibly because anxious patients may be more compulsive about their therapy. There was a trend for lower adherence with bodily pain in adults and adolescents (Table II). Adherence was 98% in those reporting no more than very mild pain ($N = 79$) compared to 92% in those reporting at least mild pain ($N = 51$). Likewise, adherence of at least 90% was reported in 95% reporting no pain ($N = 41$) compared to 69% with at least moderate pain ($N = 26$). It may be that patients find it hard to do anything, including chelation, while in pain. Alternately, patients may be avoiding chelation due to the gastrointestinal pain sometimes reported as a side effect of deferasirox. Other factors that were significant in initial bivariate analysis were side effects (adults only) and fewer transfusions in the past year.

Sixty-seven percent of patients had switched chelators since 2002, 18% more than once. Of the 199 switches from deferoxamine to deferasirox, 83% resulted in similar adherence (within 25%), 14% in greatly increased adherence, and 4% in greatly decreased adherence. Of the 49 switches from deferasirox to deferoxamine, 76% resulted in similar adherence, 18% in greatly increased adherence, and 6% in greatly decreased adherence. When restricted to patients who made only a single switch between those chelators since 2002, the numbers were similar: 14% increase and 3%

TABLE I. Baseline Demographics, Chelation Adherence, and Problems with Chelation[a] for the Thalassemia Clinical Research Network (TCRN) Thalassemia Longitudinal Cohort (TLC)

	Chelation with deferoxamine $N = 79$	Chelation with deferasirox $N = 186$
Age (years)	22.7 (12.0), 5.6–51.8	22.4 (12.4), 5.0–58.3
Gender		
Male	29 (36.7%)	96 (51.6%)
Female	50 (63.3%)	90 (48.4%)
Thalassemia diagnosis		
B-thal transfused 8+	65 (82.3%)	152 (81.7%)
B-thal transfused <8	7 (8.9%)	7 (3.8%)
E-B-thal transfused 8+	4 (5.1%)	20 (10.8%)
E-B-thal transfused <8	0 (0.0%)	3 (1.6%)
alpha-thal	3 (3.8%)	1 (0.5%)
Other	0 (0.0%)	3 (1.6%)
Race		
White	43 (55.1%)	89 (48.4%)
Asian	33 (42.3%)	84 (45.7%)
Other	2 (2.6%)	11 (6.0%)
Country		
US	49 (62.0%)	140 (75.3%)
Canada	26 (32.9%)	33 (17.7%)
UK	4 (5.1%)	13 (7.0%)
Age at first chelation		
0–4	43 (54.4%)	108 (58.1%)
5–10	24 (30.4%)	54 (29.0%)
11–17	4 (5.1%)	16 (8.6%)
18+	8 (10.1%)	8 (4.3%)
Education[b]		
< high school	0 (0.0%)	2 (4.4%)
High school degree	11 (44.0%)	16 (35.6%)
College degree	14 (56.0%)	27 (60.0%)
Marital status[b]		
Married/committed	11 (44.0%)	15 (33.3%)
Single/divorced/widowed	14 (56.0%)	30 (66.7%)
Smoking in the past year		
Yes	9 (16.1%)	19 (14.8%)
No	47 (83.9%)	109 (85.2%)
Binge drinking in the past year[c]		
Yes	10 (16.7%)	23 (16.9%)
No	50 (83.3%)	113 (83.1%)
Days per week on deferoxamine	5.7 (1.2), 1–7	
Chelation adherence[d]	91.9% (15.8), 14.3–100%	96.8% (8.7), 35.7–100%
Chelation adherence ≥ 90%	59 (74.7%)	167 (89.8%)
Chelation ≥ 5 nights/week[e]	63 (79.7%)	
Problems remembering		
Never	49 (62.0%)	109 (58.6%)
Rarely	19 (24.1%)	48 (25.8%)
Sometimes	9 (11.4%)	27 (14.5%)
Often	1 (1.3%)	1 (0.5%)
A lot	1 (1.3%)	1 (0.5%)
Problems preparing/taking[f]		
Never	64 (81.0%)	131 (71.2%)
Rarely	4 (5.1%)	36 (19.6%)
Sometimes	8 (10.1%)	15 (8.2%)
Often	2 (2.5%)	1 (0.5%)
A lot	1 (1.3%)	1 (0.5%)
Problems sticking yourself		
Never	28 (34.4%)	
Rarely	15 (19.0%)	
Sometimes	22 (27.9%)	
Often	9 (11.4%)	
A lot	5 (6.3%)	
Problems wearing pump		
Never	32 (40.5%)	
Rarely	15 (19.0%)	
Sometimes	25 (31.7%)	
Often	6 (7.6%)	
A lot	1 (1.3%)	
Side effects		
Never	25 (32.1%)	100 (54.3%)
Rarely	23 (29.5%)	45 (24.5%)
Sometimes	17 (21.8%)	28 (15.2%)
Often	8 (10.3%)	6 (3.3%)
A lot	5 (6.4%)	5 (2.7%)
Feel successful[g]		
Never	3 (4.0%)	19 (10.4%)
Rarely	6 (8.0%)	5 (2.7%)
Sometimes	13 (17.3%)	15 (8.2%)
Often	22 (29.3%)	47 (25.8%)
A lot	31 (41.3%)	96 (52.7%)

[a]Mean (SD), range for continuous variables; N (%) for categorical variables. Sample sizes vary due to missing data.
[b]For adults > 18 years only.
[c]At least 5 drinks in a single day.
[d]Percent of prescribed doses taken in the last 4 weeks.
[e]Relevant for deferoxamine only; also include those prescribed < 5 nights/weeks with 100% adherence.
[f]Questions asked about preparing deferoxamine and taking deferasirox.
[g]In the past month, have you felt successful in taking your chelator?

decrease in adherence from deferoxamine to deferasirox ($N = 153$), and 9% increase and 9% decrease in adherence from deferasirox and deferoxamine ($N = 11$). Higher adherence after a switch in chelator may reflect patient choice in switching chelators and thereafter greater adherence to the chelator of their choice. It may also indicate that patients who must switch chelators due to poor response and severe iron overload understand that adherence is necessary to avoid bad outcomes. Unfortunately, as data were collected only once for each chelator, we do not know if the increase in adherence was transient or sustained. Prior study of patients on deferasirox found that adherence of at least 90% decreased over time, from 90 to 69% over 4 years, which correlated with a rise in the proportion of patients showing mT2* deterioration [8].

In response to an open-ended question, one patient with perfect adherence to deferoxamine noted that although it can be a real hassle, especially mixing it, he/she knows it works and feels good when using it. Other less adherent patients cited difficulties with deferoxamine being painful, the injection site being sore, and being saturated, leaking and having sores. On the other hand, patients with poor adherence to deferasirox noted stomach pain and bad taste. However, many more patients wrote how much they prefer deferasirox, citing it as a "life-saver," helping in "physical and emotional health," and being able to "feel like a normal person." Those who wrote about deferasirox in relation to prior chelators noted that it is "much easier to achieve long term compliance," "way better than the other meds," and "compliance to exjade is 100%, where my compliance to desferal was about 30%." The comments received suggest that patients are extremely happy with the option of an oral chelator, but problems with administration and side effects appear to be common causes of poor adherence to both chelators. This is in keeping with an international survey [9] reporting that 58% of noncompliant patients missed a dose related to their beliefs or feelings about the chelator and 42% because of side effects.

This first study of adherence to deferasirox in clinical practice included a large, racially diverse, international sample of patients on both deferoxamine and deferasirox. However, several limitations may impact generalizability (online supplement). Adherence was collected from patient report, which could potentially be overestimated. However, the moderate correlation between adherence and ferritin and liver iron concentration (online supplement) was reassuring and may help corroborate the patient reported findings of this study. It would be worthwhile for future study to include multiple standardized methods for measuring adherence over time, especially after changes in chelator use. Assessment of other oral chelators as well as combination chelation would be of interest as well.

Methods

The Thalassemia Clinical Research Network (TCRN) is an NIH/NHLBI-funded network composed of five core thalassemia centers in North America, one in London, and their associated satellite sites. In May 2007, the TCRN launched the Thalassemia Longitudinal Cohort (TLC) study with baseline and annual collection of clinical history, results of standard-of-care procedures, and diagnoses and treatments for thalassemia and its complications. Enrollment spanned 2 years, and information on all chelator use was collected retrospectively from January 2002 through the baseline study visit. The TCRN TLC protocol was approved by the TCRN Data and Safety Monitoring Board and by the ethical review boards of all TCRN institutions. Informed consent was obtained for all participants. Eligibility for the TLC

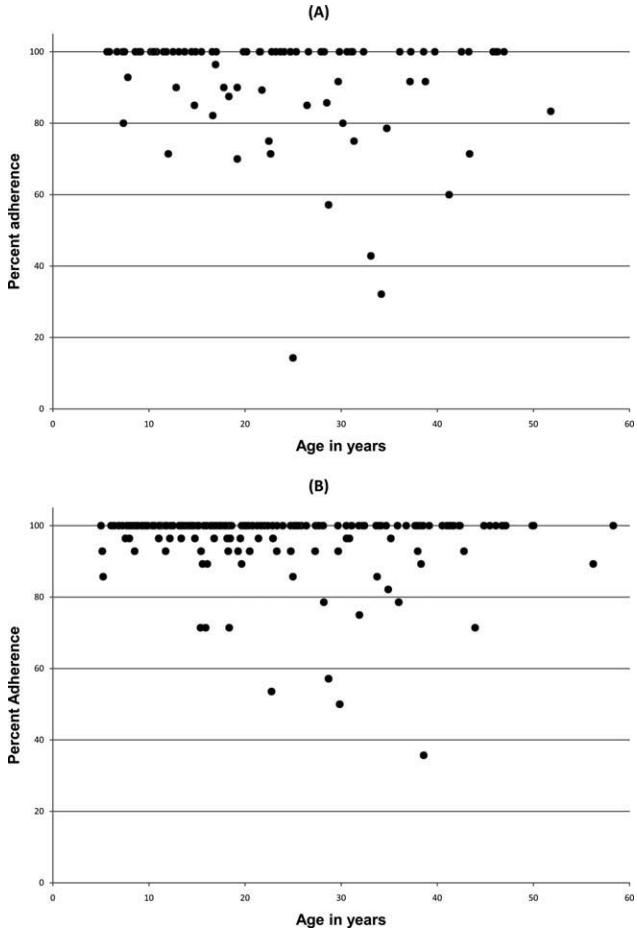

Figure 1. Chelation adherence by age to (A) deferoxamine and (B) deferasirox.

TABLE II. Predictors of Chelation Adherence[a]

Predictors of deferoxamine adherence	Slope (SE)	*P*-value
Problems sticking themselves [b]		0.056 [c]
Adults	−3.08 (1.52)	
Children	−0.31 (1.58)	
Smoking in the past year	−11.32 (5.53)	**0.045**
Predictors of deferoxamine adherence ≥90%	Odds ratio (95% CI)	*P*-value
Problems sticking themselves[b]		**0.018**[c]
Adults	0.59 [0.37, 0.95]	
Children	1.16 [0.57, 2.35]	
Predictors of deferoxamine ≥5 nights/week[d]	Odds ratio (95% CI)	*P*-value
Problems wearing pump	0.57 [0.31, 1.05]	0.071
Number of transfusions in past year	1.12 [0.98, 1.28]	0.090
Predictors of deferasirox adherence	Slope (SE)	*P*-value
Age		
Linear term	−0.63 (0.31)	**0.046**
Quadratic term	0.01 (0.01)	**0.032**
Bodily pain quality of life scale[e]	0.07 (0.04)	0.060
Depression[f]	−1.09 (0.30)	<**0.001**
Predictors of deferasirox Adherence ≥ 90%	Odds ratio (95% CI)	*P*-value
Depression[f]	0.76 [0.65, 0.90]	**0.001**

Abbreviations: SE, standard error; CI, confidence interval.
[a]predictors significant in bivariate analysis, controlling for age, at level 0.10 were entered into a multivariate analysis of covariance model with backwards elimination. For deferoxamine adherence, predictors significant in bivariate analysis were age (quadratic effect), problems wearing their pump, problems sticking themselves (adults only), smoking in the past year (yes/no), and days per week of deferoxamine use. For deferasirox adherence, predictors significant in bivariate analysis were age (quadratic effect), number of transfusions in the last year, problems with side effects (adults only), the bodily pain, role physical, general heath, and vitality quality of life scales, anxiety, and depression.
[b]Problems measured on a 1–5 scale: never through a lot. Higher numbers indicate more problems.
[c]Significant interaction between predictor and age group (adults age 18+ vs. children). Significant effect in adults only.
[d]Includes those prescribed < 5 nights/weeks with 100% adherence.
[e]Bodily pain scale of the SF-36. Higher score indicates higher quality of life, i.e., less pain.
[f]HADS depression scale. Higher score indicates increased depression.

study included patients of all thalassemia syndromes who required at least annual monitoring for end-organ injury related to thalassemia. This manuscript reports baseline data from this ongoing study. This unique large international study of thalassemia patients spanning a large age range (5–51) is the first to examine adherence to both deferoxamine and deferasirox in standard practice. Of the 428 participants in the TLC study, 314 were currently on chelation monotherapy with either deferoxamine ($N = 97$) or deferasirox ($N = 217$). Of these, 265 responded to questions on chelator adherence, 79 on deferoxamine and 186 on deferasirox.

At baseline, demographic information was collected and participants and/or their parents were surveyed about their chelation use (number of doses taken in the past week and month), problems with chelation, views about their chelation, family medical history, tobacco use, and alcohol consumption. Surveys were completed by the patient for all participants aged 16 and up. For younger participants, surveys were completed by either the patient or their parent/guardian. Surveys were completed by 103 parents/guardians and 63 children, including 54 pairs with forms completed by both child and parent. This analysis reports data from parents/guardians of participants aged 5–12 and participants aged 13 and up. Exceptions were one 10 year old with child report only and a 15-year-old with parent report only. Correlations between parent and child reports of adherence to deferoxamine or deferasirox were calculated for 49 pairs with data from both child and parent, with a excellent correlation of 0.91 for deferoxamine and 0.96 for deferasirox ($P < 0.001$ for both). For adherence to both chelators, agreement was always within 10%, and almost always within 5%. For problems with chelation, there was also a significant correlation between parent and child report for all items, except for the question on problems sticking themselves for deferoxamine ($r = 0.13$, $P = 0.56$), where 57% of pairs agreed, 29% of children reported more problems than their parents, and 14% of parents reported more problems than their children.

Participants were using a range of chelators, including deferoxamine, deferasirox, deferiprone, and combination therapy. There were insufficient numbers of patients on deferiprone or other oral therapy besides deferasirox to analyze adherence; therefore, analysis was restricted to those patients on deferoxamine and deferasirox. For this analysis, chelation adherence was defined as percent of doses administered in the last 4 weeks (patient report of chelator use as number of doses taken in the past week and month) out of those prescribed (chart review). Additional measures were calculated as well: (1) achievement of at least 90% adherence and (2) chelation with deferoxamine at least 5 nights per week (or 100% adherence if prescribed <5 nights), both of which may help avoid bad outcomes. Problems with and views about chelation were reported on a 5-point Likert scale. Problems included remembering, preparing/taking, sticking yourself and wearing the pump (deferoxamine only), side effects, and feeling successful. Views included feeling that your health depends on chelation, worries about chelation, protection from feeling worse, and disruption to life.

Participants aged 14 and older were asked to complete the hospital anxiety and depression scale (HADS) [10], as well as the SF-36v2 health survey [11], which measures health-related quality of life in 8 subscales and two summary scores: physical component and mental component. Parents of children <14 years at baseline were asked to complete the PF-28 child health questionnaire (CHQ) [12], which measures quality of life in children in 12 subscales and two summary scores (physical and mental). For all participants, transfusion frequency and volumes, chelation history, serum ferritin, and liver iron concentration (LIC by FerriScan®, MRI, SQUID, or liver biopsy) were recorded from chart review. Chelation history included chelator type, dosing, dates prescribed, and a rough estimate of adherence (0–25%, 25–49%, 50–74%, 75–100%) categorized from the medical record. The

rough estimate of adherence was not assessed systematically, but was rather whatever was available from chart review; these may reflect either an assessment by the treating physician, a record of what the patient reported during their appointment, or some combination. Exact participant assessment of adherence was collected only at the TLC study visit, but rough estimates of adherence through chart review were collected for all chelators prescribed since 2002. The rough estimates were available from the medical records of 58 participants currently using deferoxamine and 166 on deferasirox. Of the patients on deferoxamine, there was consistency between the medical records and the patient report in 78% of cases, with at most a 15% difference in another 10%. Of the patients on deferasirox, there was consistency between the medical records and the patient report in 91% of cases, with at most a 15% difference in another 3%.

Statistical analysis

Analysis of covariance was used to model predictors of adherence, controlling for age. A quadratic effect of age was used as suggested by the observed data. Predictors significant in bivariate analysis at level < 0.10 were entered into multivariate models with backward elimination. Potential predictors included age, gender, race (White, Asian, other), country (US, Canada, UK), transfusion frequency (number in last year), marital status (married/committed vs. single; adults only), education (<high school, high school degree, college degree; adults only), smoking in the last year (yes/no), consumption of five or more alcoholic drinks in a single day in the last year (yes/no), family history of thalassemia (yes/no), age at first chelation, time since first chelation, number of days per week prescribed (deferoxamine only), views about chelation, problems with chelation, quality of life scales (SF-36 for ages 14+ and CHQ for children <14; all subscales and summary scales were used), and anxiety and depression (HADS scales for ages 14+). Problems remembering to take chelation was not considered a predictor, but was found to be highly associated with adherence in confirmatory analysis. The interactions of all predictors with age group (adult vs. child) were also tested. Marital status and education data was not available from the TLC, but was available for a subset of patients ($N = 70$) also participating in the TCRN Assessment of Pain in Thalassemia Study. Association between adherence and ferritin and LIC was assessed by correlation analysis, Wilcoxon rank sum tests, and chi-squared tests. In all analyses, $P < 0.05$ was considered statistically significant, but trends for marginally significant predictors ($P < 0.10$) were examined as well.

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Additional Supporting Information may be found in the online version of this article.

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