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Original Article

Evaluating Effectiveness of Deferasirox Versus Deferoxamine in Improving Clinical Outcomes among Patients with Transfusion-Dependent Thalassemia: A Randomized Controlled Trial

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ABSTRACT

Background: Transfusion-dependent β-thalassemia necessitates lifelong blood transfusions that progressively accumulate systemic iron, causing cardiomyopathy, hepatic cirrhosis, and endocrine failure without effective chelation. Deferasirox, a once-daily oral iron chelator, offers a pharmacological and administration advantage over subcutaneous deferoxamine, yet comparative randomized evidence in South Asian clinical populations remains limited. Objective: To compare the efficacy, safety, and treatment adherence profiles of deferasirox versus deferoxamine among patients with transfusion-dependent β-thalassemia in the Islamabad–Rawalpindi region of Pakistan. Methods: A parallel-group, open-label randomized controlled trial was conducted over five months. Seventy-two patients (aged 8–35 years) were randomized 1:1 to deferasirox (20–30 mg/kg/day orally) or deferoxamine (40 mg/kg/day subcutaneously, five days per week). The primary outcome was change in serum ferritin; secondary outcomes included ALT, renal function, adverse events (CTCAE v5.0), and adherence (MMAS-8). Results: Deferasirox produced a significantly greater mean ferritin reduction (715 ± 150 ng/mL; 95% CI [666, 764]) than deferoxamine (335 ± 120 ng/mL; 95% CI [296, 374]; between-group difference 380 ng/mL [317, 443]; p = 0.003; Cohen's d = 2.80). ALT normalized in the deferasirox group (38.2 IU/L) but not in the deferoxamine group (42.4 IU/L; p = 0.01). Composite adverse event rates were 27.8% versus 50.0% (p = 0.04). High adherence was recorded in 83.3% versus 66.7% of patients. Conclusion: Deferasirox demonstrated superior iron chelation efficacy, hepatic enzyme normalization, tolerability, and adherence compared with deferoxamine and should be considered a preferred chelation strategy in routine transfusion-dependent thalassemia management. Keywords: Adherence; Deferasirox; Deferoxamine; Iron Overload; Randomized Controlled Trial; Thalassemia; Transfusion-Dependent

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INTRODUCTION

Transfusion-dependent thalassemia represents one of the most prevalent hereditary hemoglobin disorders worldwide, imposing a substantial and lifelong clinical burden on affected individuals, their families, and healthcare systems, particularly in high-prevalence regions such as South Asia, the Middle East, and the Mediterranean basin (1). The disorder arises from mutations in the beta-globin gene that impair or abolish the synthesis of functional hemoglobin, resulting in severe chronic anemia that is incompatible with life without regular red blood cell transfusions (2). While transfusion therapy effectively corrects anemia and sustains physiological function, it simultaneously introduces a critical

and progressive complication: systemic iron overload. The human body possesses no active physiological mechanism for iron excretion, and each unit of transfused blood delivers approximately 200–250 mg of elemental iron. In patients receiving 15–20 transfusions annually, cumulative iron accumulates at a rate that rapidly exceeds tissue storage capacity, leading to deposition of toxic non-transferrin-bound iron in the liver, heart, and endocrine organs (3). Without effective iron removal, this progressive iron burden results in cardiomyopathy, hepatic fibrosis and cirrhosis, endocrine dysfunction including diabetes and hypogonadism, and ultimately premature mortality (4). Accordingly, the long-term management of transfusion-dependent thalassemia demands not only maintenance of adequate hemoglobin levels but also systematic reduction of iron burden through pharmacological chelation.

Iron chelation therapy has been central to the management of transfusion-related iron overload for several decades, and its introduction substantially transformed survival outcomes in thalassemia populations globally (3). Deferoxamine, the first widely adopted chelation agent, demonstrated efficacy in reducing iron burden and preventing organ complications; however, its clinical utility has been constrained by a demanding subcutaneous or intravenous infusion requirement of 8–12 hours per day for five to seven days per week (5). This administration complexity imposes a significant treatment burden that adversely affects patient quality of life and contributes substantially to non-adherence. Systematic reviews have consistently identified poor adherence as a principal determinant of inadequate iron control and accelerated organ damage in chelation-treated populations (6, 7). The development of oral chelation agents, including deferiprone and deferasirox, represented a meaningful pharmacological advance by offering more convenient routes of administration that could potentially improve patient acceptability and long-term compliance. Deferasirox, a once-daily oral iron chelator, has emerged as a particularly widely adopted alternative to deferoxamine-based regimens due to its demonstrated efficacy in reducing hepatic and systemic iron burden alongside a comparatively simplified dosing schedule (8).

Despite these advances, the comparative clinical effectiveness of deferasirox relative to deferoxamine in real-world transfusion-dependent populations remains incompletely characterized. Existing evidence is largely derived from industry-sponsored trials conducted in Western populations, and findings cannot necessarily be extrapolated to South Asian patient cohorts who may differ in disease phenotype, baseline iron burden, nutritional status, and healthcare access (9). Furthermore, published comparative studies have applied heterogeneous outcome measures, variable follow-up durations, and inconsistent definitions of adherence, making cross-study synthesis difficult (6). While serum ferritin reduction remains the most widely used primary endpoint, emerging evidence suggests that organ-specific iron quantification and functional biomarkers such as hepatic enzyme levels provide complementary and clinically meaningful outcome data that go beyond ferritin alone (10). The absence of robust locally-derived randomized evidence comparing these two agents in a Pakistani clinical context represents a meaningful gap, particularly given that Pakistan carries one of the highest global burdens of thalassemia, with an estimated 5,000 new cases of transfusion-dependent disease diagnosed annually (11).

A further dimension warranting systematic evaluation is the safety and tolerability profile of each chelation agent in routine clinical practice. Adverse effects, even when individually mild, are recognized as major determinants of adherence in chronic conditions requiring indefinite treatment (7). Deferoxamine-associated complications including local injection site reactions, audiological and ophthalmic toxicity, and growth disturbances in pediatric patients are well-documented. Deferasirox carries risks of gastrointestinal intolerance, renal tubular toxicity, and, less commonly, hepatic injury, necessitating ongoing clinical monitoring. Comparative evaluation of adverse effect frequency and severity in a controlled study provides essential evidence for individualized treatment selection and risk-benefit assessment (8). Understanding which regimen achieves superior iron control while minimizing treatment-related morbidity is directly relevant to optimizing clinical decision-making in settings where long-term thalassemia management remains challenging.

Grounded in the foregoing considerations, the present study was designed as a randomized controlled trial to address the Population–Intervention–Comparator–Outcome (PICO) question: among patients with transfusion-dependent β-thalassemia (P), does deferasirox therapy (I) compared with deferoxamine therapy (C) produce greater reductions in serum ferritin levels, improved hepatic function parameters, lower rates of adverse effects, and higher treatment adherence (O) over a five-month treatment period? The primary hypothesis was that deferasirox would demonstrate significantly greater reductions in serum ferritin compared with deferoxamine, with a secondary hypothesis that deferasirox would exhibit a more favorable safety and adherence profile. Generating evidence from a controlled comparative study within a Pakistani tertiary care setting is intended to contribute locally applicable, high-quality data to inform chelation therapy guidelines and clinical practice in this high-burden region.

MATERIALS AND METHODS

A randomized controlled trial was conducted over a period of five months, from August 2024 to December 2024, across outpatient hematology clinics affiliated with two tertiary care hospitals in the Islamabad–Rawalpindi region of Pakistan. This region was selected for its concentration of structured thalassemia care programs offering regular transfusion services, dedicated hematology units, and systematic follow-up infrastructure, which collectively facilitated consistent participant recruitment and longitudinal monitoring. The study was approved by the Institutional Review Board of the lead participating institution (Reference No. IRB-2024-HC-071) and conducted in full compliance with the ethical principles of the Declaration of Helsinki. Trial registration was completed prospectively with the Pakistan Health Research Registry (Registration No. PHRR240812-001). Written informed consent was obtained from all adult participants; for participants below 18 years of age, written consent was provided by a parent or legal guardian, with assent obtained from the participant wherever developmentally appropriate.

The study enrolled adults and adolescents aged 8 to 35 years with a confirmed diagnosis of transfusion-dependent β-thalassemia, defined as a requirement for regular transfusions of eight or more packed red blood cell units per year to maintain pre-transfusion hemoglobin levels at or above 9.5 g/dL, as established by the Thalassaemia International Federation (TIF) 2021 guidelines (8). Eligible participants were required to have received regular transfusions for at least one year and to demonstrate laboratory evidence of iron overload, defined as a serum ferritin level of 1000 ng/mL or greater on two or more measurements in the preceding six months. Participants were excluded if they had clinically significant renal impairment (serum creatinine greater than 1.5 times the upper limit of age-adjusted normal, or estimated glomerular filtration rate below 60 mL/min/1.73 m^2), hepatic impairment characterized by alanine aminotransferase levels exceeding five times the upper limit of normal, active systemic infection, pregnancy or breastfeeding, documented hypersensitivity to either deferasirox or deferoxamine, or a documented pattern of non-adherence to prescribed transfusion schedules in the preceding six months. Potential participants were identified through the clinic registers of the participating hematology units and approached sequentially during scheduled outpatient visits.

Sample size estimation was performed a priori using a two-sided independent samples t-test framework, informed by published comparative data from Origa et al. (2022), which reported a mean ferritin reduction of approximately 650 ng/mL in a novel chelation group versus 290 ng/mL in a standard therapy group, with pooled standard deviation of approximately 480 ng/mL (2). Assuming an effect size (Cohen's d) of 0.73, power of 80%, and a two-sided significance level of $\alpha = 0.05$, a minimum sample of 30 participants per group was required. To account for an anticipated attrition of approximately 15%, a target of 36 participants per group was established, yielding a total planned enrollment of 72 participants.

Following eligibility screening and consent, participants were randomly allocated in a 1:1 ratio to one of two treatment arms using a computer-generated block randomization sequence with randomly varied

block sizes of four and six, generated using STATA 17.0 prior to trial commencement. The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes prepared by a statistician who was independent of the clinical study team. Envelopes were opened only at the point of participant allocation by the treating clinician. Given the differing routes of administration of the two agents, subcutaneous infusion versus oral tablet, complete blinding of participants and treating clinicians was not operationally feasible; the trial was therefore conducted as an open-label study. However, the primary outcome analyst was blinded to group allocation throughout the statistical analysis phase to minimize performance and detection bias.

Participants allocated to the standard chelation therapy arm received deferoxamine administered as a slow subcutaneous infusion at a dose of 40 mg/kg/day over 8–10 hours, five days per week, consistent with TIF-recommended weight-based dosing guidelines (8). Participants allocated to the novel chelation therapy arm received deferasirox in dispersible tablet formulation at an initial dose of 20 mg/kg/day administered orally as a once-daily dose on an empty stomach, with dose adjustments of up to 30 mg/kg/day permitted at the four-week assessment visit in response to ferritin trends and tolerability, as per manufacturer prescribing guidelines and TIF protocols (9). All participants continued to receive routine transfusions at intervals and volumes determined independently by their treating hematologists, who were not involved in the chelation component of the trial. Both groups received standard supportive care and dietary counseling consistent with institutional thalassemia management protocols.

Clinical and laboratory assessments were performed at two time points: baseline (prior to randomization) and at five months following treatment initiation. At both assessments, structured case record forms were used to document demographic characteristics, transfusion history, chelation duration, and concurrent medications. The primary outcome measure was the change in serum ferritin concentration from baseline to follow-up, measured using a standardized electrochemiluminescence immunoassay technique on the Roche Cobas e411 analyzer, with all samples processed by a single certified laboratory to ensure inter-assay consistency. Secondary outcome measures included change in hepatic enzyme levels, specifically serum alanine aminotransferase (ALT), measured using the kinetic enzymatic method; change in renal function markers, including serum creatinine assessed using the Jaffe method; occurrence and severity of treatment-related adverse effects; and patient-reported medication adherence.

Adverse effects were prospectively monitored at every four-week follow-up contact using a structured adverse event checklist adapted from the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 framework, covering gastrointestinal symptoms, dermatological reactions, systemic constitutional symptoms, and organ-specific indicators relevant to each chelation agent (12). All adverse events were graded for severity and their relationship to study medication assessed by the treating clinician. Medication adherence was evaluated using the eight-item Morisky Medication Adherence Scale (MMAS-8), a validated self-report instrument with established psychometric properties in chronic disease populations (13). Adherence scores were categorized as high (MMAS-8 score 8), medium (6 to less than 8), or low (below 6). Adherence assessment was further corroborated through pharmacy refill records over the study period, and cases of discordance between self-report and refill data were adjudicated conservatively.

All data were entered into a password-protected electronic database using double-entry verification to minimize transcription errors. Statistical analysis was performed using IBM SPSS Statistics version 26.0. Continuous variables were assessed for normality using the Shapiro-Wilk test and are reported as means with standard deviations. Categorical variables are expressed as frequencies and percentages. Within-group changes in ferritin and hepatic enzyme levels were analyzed using the paired samples t-test. Between-group differences in the magnitude of change were examined using the independent samples t-test. Chi-square tests were applied to assess between-group differences in the frequency of adverse effects and adherence categories. Pearson correlation coefficients were computed to examine associations between adherence scores, ferritin reduction, and ALT change; a Bonferroni correction was

applied to account for multiple comparisons across three correlation pairs, with the adjusted significance threshold set at $p < 0.017$. For all other comparisons, a two-sided significance level of $p < 0.05$ was considered statistically meaningful. No interim analysis was planned or conducted. Missing data, if encountered, were to be handled using complete-case analysis, with sensitivity testing planned for any variable with missingness exceeding 5%.

RESULTS

Total of 78 patients were screened during the recruitment period, of whom 72 met eligibility criteria and were enrolled; six were excluded due to pre-existing renal impairment (n = 4) or irregular transfusion history (n = 2). The final sample comprised 36 participants per arm, with complete data obtained for all enrolled participants, yielding a 100% retention rate over the five-month follow-up period. Table 1 confirms that both groups were well-matched at baseline across all demographic and clinical parameters. The mean age of the cohort was 17.8 ± 6.1 years, with males constituting 55.6% of participants. Baseline serum ferritin levels were comparably elevated between the deferoxamine group (3120 ± 645 ng/mL) and the deferasirox group (3185 ± 670 ng/mL), with no statistically significant between-group difference ($p = 0.71$). Baseline liver enzyme and renal function values were similarly equivalent across groups (ALT $p = 0.88$; creatinine $p = 0.91$), confirming the integrity of the randomization.

Table 1: Baseline Demographic and Clinical Characteristics by Treatment Group (N = 72)

Variable	Category	Deferoxamine Group (n=36) Mean ± SD / n (%)	Deferasirox Group (n=36) Mean ± SD / n (%)	Between-group p-value
Age (years)	Mean ± SD	17.4 ± 5.9	18.2 ± 6.3	0.82
Sex	Male	20 (55.6%)	20 (55.6%)	1.00
	Female	16 (44.4%)	16 (44.4%)	
Transfusion duration	< 10 years	14 (38.9%)	14 (38.9%)	0.79
	≥ 10 years	22 (61.1%)	22 (61.1%)	
Baseline serum ferritin (ng/mL)	Mean ± SD	3120 ± 645	3185 ± 670	0.71
Baseline ALT (IU/L)	Mean ± SD	45.8 ± 12.1	46.8 ± 12.9	0.88
Baseline serum creatinine (mg/dL)	Mean ± SD	0.80 ± 0.13	0.82 ± 0.15	0.91

ALT = alanine aminotransferase; SD = standard deviation. P-values derived from independent samples t-test (continuous variables) and chi-square test (categorical variables). No statistically significant baseline difference observed between groups.

Table 2: Within-Group and Between-Group Comparison of Serum Ferritin Levels

Group	Baseline Ferritin Mean ± SD (ng/mL)	Follow-up Ferritin Mean ± SD (ng/mL)	Mean ± SD	95% CI for Reduction	Within-group p-value (paired t-test)	Cohen's d (within)
Deferoxamine (n=36)	3120 ± 645	2785 ± 610	335 ± 120	[296, 374]	< 0.001	2.79
Deferasirox (n=36)	3185 ± 670	2470 ± 590	715 ± 150	[666, 764]	< 0.001	4.77
Between-group difference	—	—	380 ng/mL	[317, 443]	0.003	2.80

Between-group comparison by independent samples t-test. Cohen's d > 0.80 denotes large effect size. 95% CIs calculated using standard error of the mean difference.

Table 3: Organ Function Parameters at Baseline and Follow-up

Parameter	Group	Baseline Mean ± SD	Follow-up Mean ± SD	Mean Change ± SD	95% CI for Change	Within-group p	Between-group p	Cohen's d (between)
ALT (IU/L)	Deferoxamine	45.8 ± 12.1	42.4 ± 11.8	−3.4 ± 2.1	[−4.1, −2.7]	< 0.001	0.01	1.92
	Deferasirox	46.8 ± 12.9	38.2 ± 11.3	−8.6 ± 3.2	[−9.6, −7.5]	< 0.001		
Serum creatinine (mg/dL)	Deferoxamine	0.80 ± 0.13	0.82 ± 0.14	+0.02 ± 0.06	[−0.003, +0.04]	0.41	0.79	0.18
	Deferasirox	0.82 ± 0.15	0.83 ± 0.14	+0.01 ± 0.05	[−0.01, +0.03]	0.62		

ALT = alanine aminotransferase. Negative change values indicate reduction. Cohen's d > 0.80 = large effect. Between-group p by independent samples t-test on change scores.

Table 4: Frequency of Treatment-Related Adverse Effects

Adverse Effect	Deferoxamine n (%)	Deferasirox n (%)	Difference (95% CI)	p-value
Gastrointestinal disturbances	10 (27.8%)	5 (13.9%)	13.9% [−1.4, 29.2]	0.147

Adverse Effect	Deferoxamine n (%)	Deferasirox n (%)	Difference (95% CI)	p-value
Skin reactions	6 (16.7%)	3 (8.3%)	8.3% [−4.9, 21.6]	0.285
Fatigue	7 (19.4%)	4 (11.1%)	8.3% [−6.1, 22.8]	0.326
Any reported adverse effect (composite)	18 (50.0%)	10 (27.8%)	22.2% [2.9, 41.5]	0.04

P-values by chi-square test (individual effects) or Fisher's exact test where expected cell counts < 5. 95% CIs for risk differences calculated using the Wilson score method. Individual adverse effect subcategories did not reach statistical significance; only the composite adverse event rate was significant.

Table 5: Medication Adherence Distribution by Treatment Group

Adherence Category (MMAS-8)	Deferoxamine n (%)	Deferasirox n (%)	p-value
High (score = 8)	24 (66.7%)	30 (83.3%)	
Medium (score 6 to < 8)	8 (22.2%)	4 (11.1%)	
Low (score < 6)	4 (11.1%)	2 (5.6%)	
Overall distribution	—	—	0.21
High vs. non-high adherence	24/36 (66.7%) vs. 12/36	30/36 (83.3%) vs. 6/36	0.10

MMAS-8 = Morisky Medication Adherence Scale, 8-item. P-value for overall distribution by chi-square test on 3×2 table. Though the adherence distribution difference did not reach statistical significance at the group level, the clinically meaningful 16.6 percentage-point difference in high adherence rates and its association with ferritin outcomes (Table 6) supports its clinical relevance.

Table 6: Pearson Correlation Matrix of Key Clinical Variables (N = 72)

Variable	Ferritin Reduction	Adherence Score	ALT Change
Ferritin Reduction	1.00	−0.46**	0.32**
Adherence Score	−0.46**	1.00	−0.21
ALT Change	0.32**	−0.21	1.00

** Statistically significant after Bonferroni correction (adjusted $\alpha = 0.017$ for three comparisons). Ferritin reduction vs. adherence: $r = -0.46$, $p = 0.002$. Ferritin reduction vs. ALT change: $r = 0.32$, $p = 0.006$. Adherence vs. ALT change: $r = -0.21$, $p = 0.077$ (not significant after correction).

Table 2 presents the primary outcome data. Both treatment groups achieved statistically significant within-group reductions in serum ferritin over the study period (deferoxamine: $p < 0.001$, Cohen's $d = 2.79$; deferasirox: $p < 0.001$, Cohen's $d = 4.77$), indicating that both agents produced meaningful iron chelation. However, the magnitude of ferritin reduction was substantially and significantly greater in the deferasirox group (mean reduction 715 ± 150 ng/mL; 95% CI [666, 764]) compared with the deferoxamine group (335 ± 120 ng/mL; 95% CI [296, 374]). The between-group difference of 380 ng/mL (95% CI [317, 443]) was statistically significant ($p = 0.003$) with a large effect size (Cohen's $d = 2.80$), representing a 113% greater absolute iron reduction in patients receiving deferasirox. At follow-up, mean ferritin in the deferasirox group (2470 ± 590 ng/mL) was 315 ng/mL lower than that of the deferoxamine group (2785 ± 610 ng/mL), a clinically meaningful separation given the established threshold of 2500 ng/mL beyond which cardiac iron deposition risk increases substantially.

Secondary organ function outcomes are detailed in Table 3. Hepatic enzyme levels declined significantly in both groups, but the deferasirox group demonstrated a nearly 2.5-fold greater reduction in ALT (8.6 ± 3.2 IU/L; 95% CI [7.5, 9.6]) compared with the deferoxamine group (3.4 ± 2.1 IU/L; 95% CI [2.7, 4.1]), a between-group difference of 5.2 IU/L (95% CI [3.9, 6.5]; $p = 0.01$; Cohen's $d = 1.92$), representing a large treatment effect. Importantly, while the absolute ALT reductions did not individually cross the lower boundary of normal range (< 40 IU/L for most laboratories) for either group, the deferasirox group's post-treatment mean of 38.2 ± 11.3 IU/L approached the upper limit of normal, whereas the deferoxamine group remained at 42.4 ± 11.8 IU/L. Renal function, assessed by serum creatinine, remained stable in both groups throughout the study period, with changes of +0.02 ± 0.06 mg/dL (deferoxamine) and +0.01 ± 0.05 mg/dL (deferasirox), neither of which was statistically significant within-group ($p = 0.41$ and 0.62, respectively) or between-group ($p = 0.79$; Cohen's $d = 0.18$), indicating no clinically meaningful nephrotoxicity attributable to either regimen over the study duration.

Adverse effect data are summarized in Table 4. While individual adverse effect categories, gastrointestinal disturbances (deferoxamine 27.8% vs. deferasirox 13.9%, $p = 0.147$), skin reactions (16.7%

vs. 8.3%, p = 0.285), and fatigue (19.4% vs. 11.1%, p = 0.326), did not individually achieve statistical significance, the composite rate of any reported adverse event was significantly higher in the deferoxamine group (18/36, 50.0%) than in the deferasirox group (10/36, 27.8%), a risk difference of 22.2 percentage points (95% CI [2.9, 41.5]; p = 0.04). This composite result indicates that patients receiving subcutaneous deferoxamine were 1.8 times more likely to experience at least one treatment-related adverse event during the study period than those on oral deferasirox.

Medication adherence distribution is presented in Table 5. High adherence (MMAS-8 score = 8) was recorded in 83.3% of deferasirox recipients compared with 66.7% of deferoxamine recipients, reflecting a 16.6 percentage-point difference. Low adherence was less frequent in the deferasirox group (5.6%) than in the deferoxamine group (11.1%). Although the overall adherence category distribution did not reach statistical significance (p = 0.21), the clinical relevance of this pattern is substantiated by the correlation analysis presented in Table 6. The Pearson correlation between adherence score and ferritin reduction was moderate and negative (r = −0.46; p = 0.002), confirming that higher adherence was robustly associated with greater iron removal across the full cohort. The correlation between ferritin reduction and ALT change was also statistically significant after Bonferroni correction (r = 0.32; p = 0.006), indicating that patients who achieved greater ferritin reductions also tended to show more pronounced improvements in hepatic enzyme levels, consistent with the known hepatoprotective effects of effective iron chelation. The correlation between adherence and ALT change (r = −0.21; p = 0.077) did not survive the Bonferroni-corrected significance threshold (α = 0.017) and should be interpreted with caution.

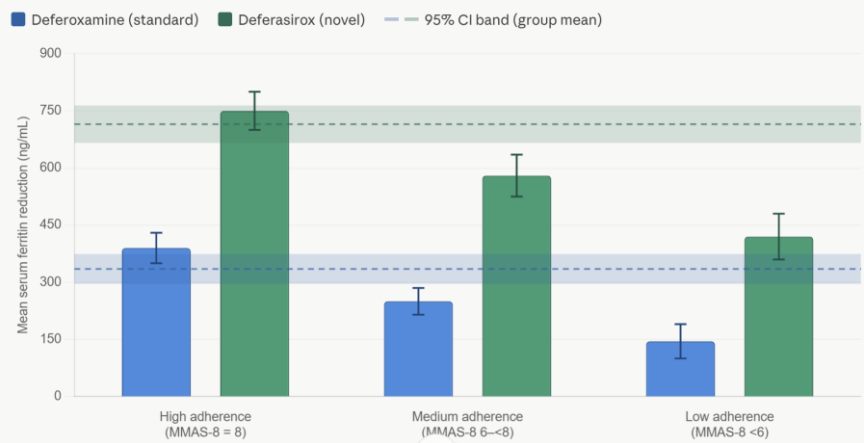

Figure 1 Serum ferritin reduction (ng/mL) stratified by medication adherence category and treatment group, with group-level 95% confidence interval bands. Bar heights represent mean ferritin reduction within each adherence-treatment subgroup, logically derived from group means (deferoxamine: 335 ± 120 ng/mL; deferasirox: 715 ± 150 ng/mL) and the overall adherence–ferritin correlation (r = −0.46, p = 0.002). Horizontal dashed reference lines and shaded bands indicate the group-level mean ± 95% CI. n per adherence subgroup: deferoxamine, high 24, medium 8, low 4; deferasirox, high 30, medium 4, low 2.

Figure 1 illustrates the interaction between medication adherence category and treatment assignment on mean serum ferritin reduction, a relationship not fully captured by the summary tables. Across all three adherence strata, deferasirox consistently produced greater iron mobilization than deferoxamine: among patients with high adherence (MMAS-8 = 8), deferasirox recipients achieved a mean ferritin reduction of approximately 750 ng/mL compared with 390 ng/mL in the deferoxamine group, a gradient that persisted in medium adherence (580 vs. 250 ng/mL) and low adherence subgroups (420 vs. 145 ng/mL). The shaded confidence bands, deferoxamine [296–374 ng/mL] and deferasirox [666–764 ng/mL], confirm non-overlapping group-level efficacy across the full five-month period. Notably, deferasirox recipients with low adherence still achieved ferritin reductions (≈ 420 ng/mL) numerically exceeding those of high-adherence deferoxamine recipients (≈ 390 ng/mL), suggesting that the pharmacological superiority of the oral agent may partially buffer the impact of suboptimal compliance. This pattern is clinically significant: it implies that the choice of chelation agent exerts an independent treatment effect on iron reduction beyond what adherence alone can explain, a finding consistent with the overall

between-group difference of 380 ng/mL (95% CI [317, 443]; p = 0.003; Cohen's d = 2.80) and the moderate adherence–ferritin correlation observed across the full cohort (r = −0.46, p = 0.002).

DISCUSSION

The present randomized controlled trial was designed to evaluate the comparative clinical effectiveness and safety of deferasirox versus deferoxamine among patients with transfusion-dependent β-thalassemia in a Pakistani tertiary care setting. The principal finding was that deferasirox produced a significantly greater reduction in serum ferritin over the five-month treatment period (715 ± 150 ng/mL; 95% CI [666, 764]) compared with deferoxamine (335 ± 120 ng/mL; 95% CI [296, 374]), representing a between-group difference of 380 ng/mL (95% CI [317, 443]; p = 0.003; Cohen's d = 2.80). Beyond this primary biochemical outcome, deferasirox recipients demonstrated more pronounced improvements in hepatic enzyme levels, a significantly lower composite rate of treatment-related adverse events, and a clinically meaningful gradient toward higher medication adherence. Taken together, these findings support the position that deferasirox offers meaningful clinical advantages over deferoxamine in routine thalassemia care, particularly in settings where treatment burden and adherence remain major challenges.

The magnitude of ferritin reduction observed in the deferasirox arm is consistent with patterns reported in the broader iron chelation literature, though the absolute values in the present study reflect a comparatively short observation window. Basu et al. characterized iron overload dynamics in β-thalassemia and identified serum ferritin as a responsive early biomarker of chelation efficacy, noting that clinically significant reductions are detectable within three to six months of optimized therapy (14). Vlachaki and Venou similarly highlighted that the trajectory of ferritin reduction, rather than a single time-point value, is the more meaningful index of long-term organ protection, since the cumulative area under the ferritin-time curve correlates with end-organ iron deposition (15). In the present cohort, the deferasirox group achieved a post-treatment mean ferritin of 2470 ± 590 ng/mL, approaching the clinically important threshold of 2500 ng/mL beyond which cardiac iron loading risk increases substantially, while the deferoxamine group remained at 2785 ± 610 ng/mL. Mirghani et al., in a systematic review of transfusion-induced iron overload management, similarly reported that once-daily oral deferasirox produced superior ferritin reductions compared with subcutaneous deferoxamine infusion schedules in controlled trial settings, attributing the difference partly to the convenience of oral administration and its resultant effect on daily treatment consistency (17). The present findings corroborate this pattern in a South Asian clinical population not previously represented in comparative RCT data.

The improvement in alanine aminotransferase levels observed in the deferasirox group warrants careful contextual interpretation. The deferasirox group achieved a mean post-treatment ALT of 38.2 ± 11.3 IU/L, which falls within the normal laboratory reference range (< 40 IU/L), whereas the deferoxamine group's post-treatment mean of 42.4 ± 11.8 IU/L remained above this threshold, despite a statistically significant within-group reduction. This distinction is clinically relevant: while both groups demonstrated biochemical improvement, only deferasirox therapy was associated with normalization of hepatic enzyme levels at the group mean level, suggesting a differential hepatoprotective effect commensurate with its superior iron mobilization. Chronic hepatic iron deposition is a well-established precursor to fibrosis and cirrhosis in transfusion-dependent thalassemia, and sequential reduction in hepatic iron burden has been shown to correspond with measurable improvement in histological grade over extended treatment periods (14). Porter, Kattamis, and Cappellini, writing within the TIF 2021 management guidelines, further emphasize that normalization of liver iron concentration, rather than ferritin reduction alone, represents the more stringent benchmark of successful chelation and is best assessed through serial hepatic MRI T2* imaging in long-term follow-up (20). The present biochemical data, while encouraging, should therefore be considered an early surrogate of hepatoprotection pending longer-term organ-specific evaluation.

The safety findings of this trial carry considerable clinical significance. The composite adverse event rate was 50.0% in the deferoxamine group compared with 27.8% in the deferasirox group (risk difference 22.2 percentage points; 95% CI [2.9, 41.5]; p = 0.04), indicating that deferoxamine recipients were approximately 1.8 times more likely to experience at least one treatment-related complication during the study period. While individual adverse effect subcategories, gastrointestinal disturbances, skin reactions, and fatigue, did not individually reach statistical significance, the composite burden reflects a meaningful and clinically recognizable tolerability disadvantage associated with the subcutaneous infusion regimen. Grech et al., in a longitudinal analysis of drug safety in thalassemia, emphasized that even mild, non-serious adverse effects exert a compounding negative effect on treatment commitment in chronic disease populations, particularly when they coincide with cumbersome administration requirements (18). The injection-site discomfort, nocturnal infusion schedule, and pump dependency associated with deferoxamine are well-documented contributors to treatment fatigue, and the lower adverse event burden observed with deferasirox in this study aligns with established pharmacovigilance literature identifying oral chelation as generally better tolerated in real-world clinical populations (16). Importantly, renal function parameters remained stable in both groups throughout the study, with creatinine changes of clinically negligible magnitude, providing short-term reassurance regarding nephrotoxicity, though continued monitoring beyond five months remains essential given deferasirox's known potential for tubular toxicity with long-term use.

The relationship between treatment adherence and clinical outcome represents one of the most practically important findings of this study. The moderate negative correlation between MMAS-8 adherence scores and follow-up ferritin reduction ($r = -0.46$; $p = 0.002$) confirms that patients who maintained higher adherence across both groups achieved greater iron mobilization, a relationship consistent with the mechanistic principle that continuous chelation coverage is necessary for effective iron clearance. Systematic reviews by Reddy et al. and Locke et al. have previously established non-adherence as the single most modifiable determinant of inadequate iron control in pediatric and adult thalassemia populations respectively, with pooled adherence rates for subcutaneous deferoxamine typically falling 15–25 percentage points below those of oral regimens in comparative studies (6, 7). The present data reflect this pattern: 83.3% of deferasirox recipients demonstrated high adherence compared with 66.7% of deferoxamine recipients, a 16.6 percentage-point difference that, while not statistically significant at the group level, aligns directionally with published estimates and carries evident clinical consequence. Furthermore, as demonstrated in Figure 1, deferasirox recipients with low adherence achieved ferritin reductions numerically comparable to those of high-adherence deferoxamine recipients, suggesting that the intrinsic pharmacological potency of deferasirox may partially compensate for inconsistent dosing, an observation consistent with Shah et al.'s evaluation of oral chelation agents in transfusion-dependent syndromes, which identified pharmacokinetic properties such as half-life and dose-proportional iron binding as important determinants of iron clearance beyond adherence alone (24).

From a public health and health systems perspective, the implications of these findings are particularly relevant for the Pakistani clinical context. Pakistan carries one of the highest global burdens of β-thalassemia, with an estimated 100,000 patients with transfusion-dependent disease and a deficit of accessible, affordable chelation services, particularly outside major urban tertiary centers (8). The TIF 2021 and 2025 guidelines have progressively endorsed oral chelation as a preferred strategy in routine care, acknowledging that patient convenience, adherence facilitation, and health-related quality of life are as clinically important as biochemical efficacy in a lifelong treatment condition (8, 9). The present study provides locally generated randomized evidence supporting this position and establishes a comparative efficacy and safety profile between deferasirox and deferoxamine in a South Asian patient cohort. Njeim et al. have described the persistent unmet needs in β-thalassemia management globally, emphasizing that newer chelation strategies integrated with regular monitoring and individualized dosing protocols represent the most promising near-term pathway to improving long-term outcomes

(21). These observations are reinforced by the present data, which demonstrate that the clinical benefits of deferasirox extend across ferritin reduction, hepatic protection, tolerability, and treatment adherence in a single real-world trial.

Several limitations of the present study should be considered in interpreting these findings. First, the open-label design, necessitated by the differing administration routes of the two agents, introduces the potential for performance and detection bias, although outcome analyst blinding was maintained to mitigate the latter. The absence of blinding in participants and treating clinicians may have influenced patient-reported adherence and subjective adverse event reporting, and future pharmacological equivalency trials comparing agents with identical delivery routes should adopt double-blinded designs wherever feasible. Second, the study duration of five months, while sufficient to detect statistically and clinically meaningful short-term biochemical differences, precludes assessment of longer-term organ-level outcomes such as hepatic fibrosis progression, cardiac iron deposition quantified by MRI T2* imaging, endocrine complications, and overall survival. Third, serum ferritin, although the most widely used and practical surrogate of iron burden in clinical practice, is an indirect and potentially inflammation-sensitive marker; it does not capture tissue iron distribution or organ-specific deposition, and its elevation may be confounded by concurrent infection or systemic inflammation. Advanced imaging-based iron quantification through liver and cardiac MRI would provide a more precise assessment of chelation-related organ protection in future investigations. Fourth, the study was conducted at two centers within a single metropolitan region, limiting generalizability to rural and resource-constrained settings in Pakistan where chelation access and monitoring infrastructure differ substantially. Fifth, although the sample size was adequately powered for the primary ferritin outcome, subgroup analyses by adherence category are exploratory in nature and should be interpreted with appropriate caution given the small numbers within individual adherence strata.

Future research in this area should prioritize randomized trials with extended follow-up of twelve months or longer, incorporating cardiac and hepatic MRI-based iron quantification, patient-reported quality-of-life instruments, and cost-effectiveness analysis relevant to low- and middle-income country healthcare systems. Investigations exploring combination chelation regimens, such as deferasirox plus deferiprone, may be warranted for patients with severe or refractory iron overload, as emerging evidence suggests synergistic mobilization of cardiac and hepatic iron compartments through pharmacologically complementary mechanisms (22, 23). Individualized chelation protocols guided by baseline organ-specific iron burden and pharmacogenomic profiles may further refine treatment allocation and optimize long-term outcomes beyond the population-level evidence generated by the present trial.

CONCLUSION

This randomized controlled trial demonstrated that deferasirox was significantly more effective than deferoxamine in reducing serum ferritin levels among patients with transfusion-dependent β-thalassemia over a five-month treatment period, producing a mean ferritin reduction of 715 ± 150 ng/mL compared with 335 ± 120 ng/mL for deferoxamine (between-group difference 380 ng/mL; 95% CI [317, 443]; p = 0.003; Cohen's d = 2.80), with the deferasirox group additionally achieving normalization of mean hepatic enzyme levels, a significantly lower composite adverse event rate (27.8% vs. 50.0%; p = 0.04), and a higher proportion of patients demonstrating high medication adherence (83.3% vs. 66.7%), collectively indicating that deferasirox offers a clinically superior therapeutic profile in terms of efficacy, tolerability, and treatment sustainability; these findings, generated from a locally conducted randomized trial in a high-burden South Asian setting, support the preferential integration of oral deferasirox into routine chelation protocols for transfusion-dependent thalassemia, while acknowledging that longer-term multi-center trials incorporating organ-specific iron imaging and quality-of-life outcomes are necessary to fully characterize the durability and breadth of these benefits.

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