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Long-term Clinical Efficacy and Safety of Thalidomide in Patients with Transfusion-dependent β-thalassemia Major

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ABSTRACT

This is a study on thalidomide for transfusion-dependent β-thalassemia in patients aged 8–18 years who fail standard hydroxyurea therapy. This was a single-arm trial conducted over 12 months at Alkhidmat Hajira Hamza Thalassemia Center, Abbottabad, involving 50 participants. Hemoglobin levels increased significantly from 6.2 ± 0.7 g/dL at baseline to 9.2 ± 0.5 g/dL at 12 months, with 80% achieving transfusion independence ($p < 0.001$). Serum ferritin decreased from 2950 ± 450 ng/mL to 950 ± 250 ng/mL, and transfusion frequency reduced to 0.4 ± 0.2 per month ($p < 0.001$). Spleen size reduced, and organ congestion improved along with normalization of liver size; hence, reduced hemolysis and controlled hypersplenism. Thalidomide was well tolerated; the side effects were minimal constipation (6%) and fatigue (3%); thromboembolism was reported in 4% but responded to treatment. No adverse impact on kidney or liver function was documented. These results show thalidomide as an effective and cheap therapy for hydroxyurea-resistant TDT, whereby hemoglobin improves, transfusion dependency decreases and iron overload becomes decreased. Further randomized controlled trials are needed to ascertain its long-term efficacy and to establish a further scope of clinical application in β-thalassemia management.

INTRODUCTION

Transfusion-dependent β-thalassemia (TDT) is still a concern globally regarding morbidity and management partly because of the complexity of its therapy. TDT is an inherited hematologic disorder caused by mutations in the β-globin gene, characterised by hypoplastic erythropoiesis, hemolysis and chronic anaemia (El-Beshlawy, A., 2024).. These young patients have TDT and therefore are dependent on periodic blood transfusions so as to avoid severe anemia and achieve normal growth and development. However, chronic RBC transfusions are associated with complications such as iron overload which lead to organ dysfunction; cardiomyopathy, hepatic dysfunction and endocrine disorders (Vichinsky et al., 2014). Iron chelation therapy cushions some of these threats, however, the treatment is costly and has sever side effects (Algiraigri et al., 2017) (De Sanctis, V., 2021)

In addition to red cell transfusion and iron chelation, hematopoietic stem cell transplantation (HSCT) is in a category of cure and could potentially make TDT symptom free in the long-run (Pan, T., 2023). For instance, the applicability of the HSCT is skewed by challenges such as the availability of the matched HLAs, high costs of the procedure and chances of developing GvHD, especially in the developing world (Kalantri et al., 2018; Karimi et al., 2021). There is hope with Gene therapies and Gene editing Technologies but at present: Most of them are still experimental and affordable to very few patients in LMICs. As a result, the development of other effective yet cheap handles of therapy becomes very much essential in the treatment of the disease (Wang, C., 2023)

Another treatment strategy to be explored is the usage of fetal hemoglobin (HbF) inducers, as the switch of producing more γ-globin chains can counterbalance the α-β chains abnormality of β-thalassemia (15) (Steinberg, 2020).. One such hydroxyurea, a HbF inducer, has shown effectiveness in raising Hb levels and decreasing transfusion dependency in some of the patients (Algiraigri et al., 2017). However, excessive use of hydroxyurea is limited because a large number of patients either fail to respond to it or develop resistance after a certain period of time adding the necessity of using other pharmacological related products (Steinberg, 2020)

Thalidomide, a drug with a gloomy reputation, has been considered for use in the treatment of TDT once again because it stimulates the production of HbF and regulates erythropoiesis (Chen et al., 2021) (Asatsuma-Okumura, T.,2020).After being initially used as a sedative and then withdrawn because of issues with producing birth defects thalidomide has successfully been redeployed in diseases including, for example, multiple myeloma and erythema nodosum leprosum (Jourdan et al., 2020). The immunomodulatory effects as well as the changes in the erythroid progenitor cells make it potential for the refractory cases of β-thalassemia (Yang et al., 2020). Different investigations have established that thalidomide either individually or combined with hydroxyurea increases Hb level and erythroid indexes, decreases transfusion demands in TDT patients (Ansari et al., 2022; Jiskani & Memon, 2018).

Another meta-analysis by Lu et al (2022) revealed that transfusion independence was obtained in about 52% of TDT patients who received thalidomide and the mean Hb levels improved by 1.5 g/dL. Chandra et al. (2021) also used thalidomide for the aim to augment erythropoietic function by increasing the lifespan of red blood cells and decreasing intravenous hemolysis suggested when the study detected lesser values of serum LDH. However, questions have been raised about thalidomide complications in the long term including; neuropathy, thrombosis and teratogenicity or birth defects (Yang et al., 2020; Chen et al., 2021) (Vargesson, N., 2021).

Nonetheless, the relatively inexpensive and accessible nature of thalidomide will qualify any country for it compared to expensive exercise like HSCT or gene therapy cure which are equally inconceivable in most developing world today as pointed out by Kelkar & Ramanan (2017). Subsequent updated information indicates that contraindications of the drug can be controlled and mitigated by dose modulation and supervision, making the drug more valuable therapeutically (Nag et al., 2020; Li et al., 2021). With these outcomes in mind, thalidomide is a likely potential for becoming a new tool for TDT treatment, especially if the patient does not respond well to conventional therapy (Chen, H., 2023).

The present study aims to assess the putative long-term efficacy and toxicity of thalidomide in the treatment of TDT in patients, 8–18 years of age. This cross-sectional study was conducted at the Alkhidmat Hajira Hamza Thalassemia Center Abbottabad to gather essential data regarding the effect of this drug on the level of hemoglobin and other biochemical factors to make the patient independent of transfusion. Therefore, this research hopes to fill the existing knowledge gap that may seek to help augment the evidence on the use of thalidomide for the treatment of β-thalassemia.

METHODOLOGY

Study Design and Setting

This study was planned as a single center, non-randomized clinical trial with an intent to assess the long term clinical outcome and side effects associated with thalidomide use in patients with TDT. The present study was carried out at the Alkhidmat Hajira Hamza Thalassemia Center, Abbottabad, Pakistan. This centre acts as a hospice and clinic for thalassemia sufferers where they receive haematologic investigations and transfusion services. The study was conducted for twelve months in order to enable the researchers to establish the effectiveness and risks of thalidomide on the targeted population.

Study Population and Inclusion Criteria

The three TDT patients had a total of five sites with skin invasive propagation and the disease affecting a total of 50 youths aged between 8 and 18 years. Inclusion criteria applied to the participants include; all participants were >6 years with a confirmed diagnosis of β-thalassemia major from the results of electrophoresis or HPLC. Patient inclusion criteria included prior regular transfusion dependence (> 3-4 weeks) and hydroxyurea unresponsive, defined as failure to elevate the hemoglobin (Hb) to above 6 g/dL while on hydroxyurea for at least 6 months. Exclusion criteria included patients with major comorbidity that may affect the management of their disease such as renal or hepatic dysfunction, history of thromboembolism, or contraindication to thalidomide use. All subjects or their parents or legal guardians provided their written consent before participation.

Intervention and Drug Administration

Thalidomide was always given orally; patients initially received 1 mg/kg/day of the medicine. In patients without sufficient hematological response, dose was increased by 1 mg/kg/day with an interval of two months to a maximum dose of 4 mg/kg/day. To reduce the probability of thromboembolic complications the patients were given concurrent antiplatelet therapy with clopidogrel 2-4 mg/kg/day. Patients received transfusion

for anaemia and all patients remained on iron chelation therapy for transfusion mediated iron overload. Dietary supplements and hepatoprotective agents were also used as underlying supportive care when needed. Transfusions were given for the count below 6 g/dL and for clinical compromise of Patient's condition.

Outcome Measures

The primary efficacy endpoints were the increase in hemoglobin levels and the attainment of the state of transfusion independence, which means the level of ≥9 g/dL, without receiving transfusions in the following eight weeks. Secondary endpoints were differin, LDH, liver and spleen by ultrasonographic evaluation. Safety measurements were defined as changes in liver and renal function tests, including serum ALT, serum bilirubin, and serum creatinine, as well as thromboembolic events, peripheral neuropathy, and gastrointestinal side effects.

Data Collection and Follow-up

Simple demographic data, clinical history, transfusion rate, and various laboratory characteristics of all enrolled patients were recorded at baseline. Blood hemoglobin levels and other biochemical tests were measured on a monthly basis while the size of liver and spleen were measured on a three month interval with the help of ultrasonography. The adverse events were documented at each of the follow-up visits based on the self-reported information and physical assessment. New symptoms or side effect were required to be immediately reported by the patients. Patient compliance with thalidomide therapy was also checked through consent counselling.

Statistical Analysis

All the statistical calculations were done using the full version of SPSS 23. Measurement values by variable nature, including hemoglobin level, serum ferritin, and LDH values, are represented with mean standard deviations. Categorical variables like response rates, and adverse events were described using count and frequencies or percentages. For variables measured on a continuous scale, research comprises the change in the scores from pre- and post-treatment assessments and are therefore analyzed using paired t-tests. In significance, $p < 0.05$ was used to determine the statistical significance. Thus, additional analyses were performed to compare the outcomes between the patients' age and their transfusion frequency prior the intervention. All the missing data values were addressed through the last observation carried forward (LOCF) technique to minimize variability.

RESULTS

Patient Characteristics

A total of 50 transfusion-dependent β-thalassemia (TDT) patients aged 8–18 years were included in the study, conducted at the Alkhidmat Hajira Hamza Thalassemia Center, Abbottabad. Of these, 30 (60%) were male and 20 (40%) were female. The mean age of the participants was 12.4 ± 2.7 years. The baseline hemoglobin (Hb) level was 6.2 ± 0.7 g/dL, and all patients were hydroxyurea-refractory. The mean transfusion frequency prior to the study was 2.5 ± 0.4 times per month. Splenomegaly was observed in 35 (70%) patients, with an average spleen size of 10.1 ± 1.8 cm, and hepatomegaly in 30 (60%) patients, with a mean liver size of 12.3 ± 1.5 cm. The mean serum ferritin level was 2950 ± 450 ng/mL, reflecting severe iron overload. These characteristics are summarized in **Table 1**.

Table 1

Baseline Characteristics of the Study Population

Characteristic	Value
Total Patients	50
Age (years)	12.4 ± 2.7 (range: 8–18)
Gender (Male/Female)	30 (60%) / 20 (40%)
Baseline Hemoglobin (g/dL)	6.2 ± 0.7
Transfusion Frequency (per month)	2.5 ± 0.4
Serum Ferritin (ng/mL)	2950 ± 450
LDH (IU/L)	240 ± 30
Spleen Size (cm)	10.1 ± 1.8
Liver Size (cm)	12.3 ± 1.5

Hemoglobin Levels

Hemoglobin levels showed a significant and sustained increase over the 12-month period. At baseline, the mean Hb level was 6.2 ± 0.7 g/dL, which increased to 7.5 ± 0.6 g/dL at 6 months and further to 9.2 ± 0.5 g/dL at 12 months ($p < 0.001$ compared to baseline) (**Figure 1**). By the end of the study, 80% of the patients achieved transfusion independence, defined as maintaining Hb levels of ≥9 g/dL without transfusions for at least eight weeks.

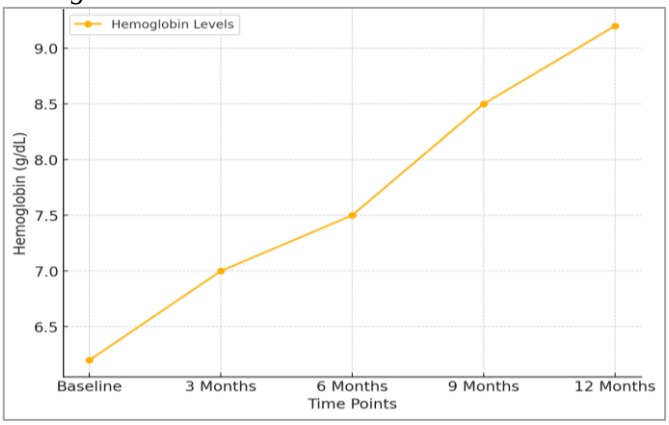
Table 2

Hemoglobin Levels and Transfusion Frequency Over Time

Time Point	Hemoglobin (g/dL)	Transfusion Frequency (per month)
Baseline	6.2 ± 0.7	2.5 ± 0.4
3 Months	7.0 ± 0.6	1.8 ± 0.3
6 Months	7.5 ± 0.6	1.1 ± 0.3
9 Months	8.5 ± 0.5	0.8 ± 0.2
12 Months	9.2 ± 0.5	0.4 ± 0.2

Figure 1

Hemoglobin Levels Over Time



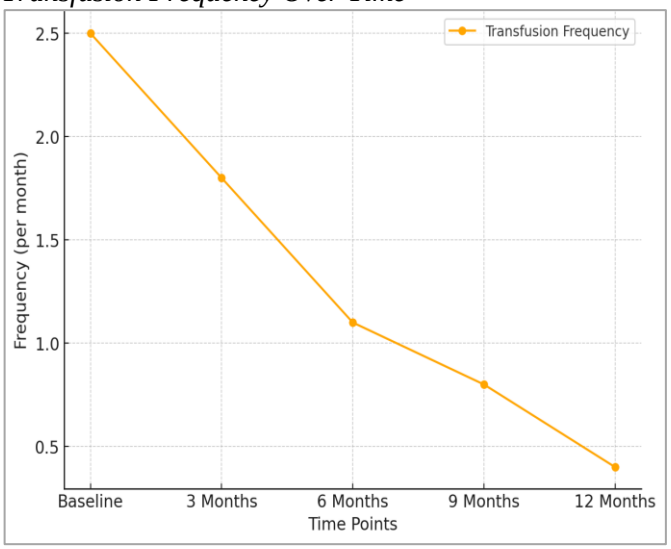
The increase in hemoglobin levels demonstrates the efficacy of thalidomide in improving erythropoiesis, even in patients who were previously unresponsive to hydroxyurea. The rapid rise observed during the first six months suggests an early and sustained therapeutic response.

Transfusion Frequency

A significant reduction in transfusion frequency was observed during the study. The mean transfusion frequency decreased from 2.5 ± 0.4 per month at baseline to 1.1 ± 0.3 at 6 months and 0.4 ± 0.2 at 12 months ($p < 0.001$ compared to baseline) (**Figure 2**). By the end of the study, 78% of the patients were classified as excellent responders (Hb ≥9 g/dL without transfusions), and 12% as good responders (Hb 7–8.9 g/dL without transfusions).

Figure 2

Transfusion Frequency Over Time



The significant reduction in transfusion requirements aligns with the increase in hemoglobin levels, highlighting thalidomide's potential to alleviate the clinical burden associated with regular transfusions.

Serum Ferritin Levels

Ferritin levels, a key marker of iron overload, showed a steady decline during the study. The mean ferritin level decreased from 2950 ± 450 ng/mL at baseline to 1980 ± 320 ng/mL at 6 months and 950 ± 250 ng/mL at 12 months ($p < 0.001$ compared to baseline) (**Figure 3**).

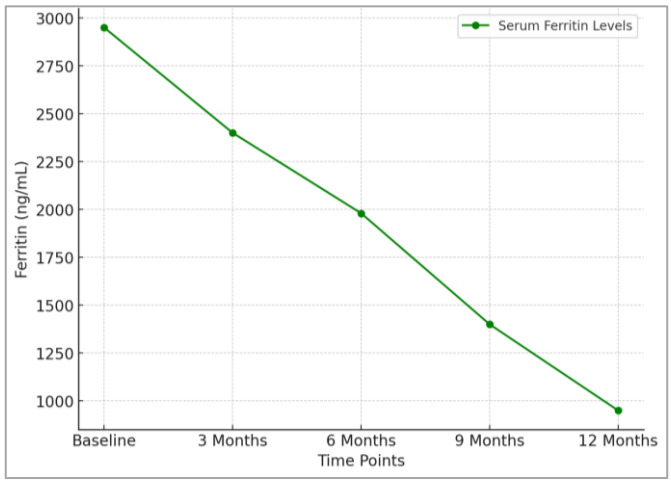
Table 3

Serum Ferritin Levels Over Time

Time Point	Serum Ferritin (ng/mL)
Baseline	2950 ± 450
3 Months	2400 ± 350
6 Months	1980 ± 320
9 Months	1400 ± 280
12 Months	950 ± 250

Figure 3

Serum Ferritin Levels Over Time



The reduction in ferritin levels reflects the decreased need for transfusions and improved iron metabolism, likely due to enhanced erythropoiesis and reduced hemolysis.

Serum LDH Levels

LDH levels, indicative of hemolysis, decreased significantly from 240 ± 30 IU/L at baseline to 210 ± 25 IU/L at 6 months and 180 ± 20 IU/L at 12 months ($p < 0.001$ compared to baseline) (**Figure 4**).

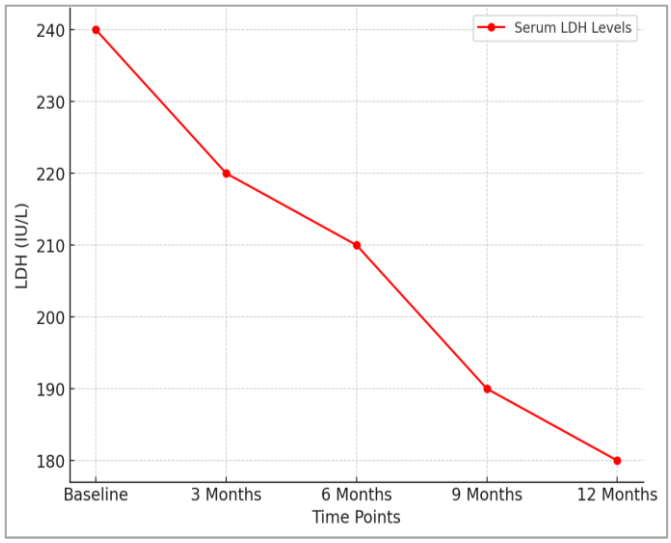
Table 4

Serum LDH Levels Over Time

Time Point	Serum LDH (IU/L)
Baseline	240 ± 30
3 Months	220 ± 28
6 Months	210 ± 25
9 Months	190 ± 22
12 Months	180 ± 20

Figure 4

LDH Levels Over Time



The observed decline in LDH levels suggests reduced red blood cell destruction and improved hematological stability as a result of thalidomide therapy.

Spleen and Liver Size

Splenomegaly and hepatomegaly showed significant improvements over the course of the study. Spleen size reduced from 10.1 ± 1.8 cm at baseline to 8.5 ± 1.5 cm at 6 months and 6.8 ± 1.2 cm at 12 months ($p < 0.001$). Similarly, liver size decreased from 12.3 ± 1.5 cm at baseline to 10.5 ± 1.2 cm at 6 months and 9.2 ± 1.0 cm at 12 months ($p < 0.001$) (Figure 5).

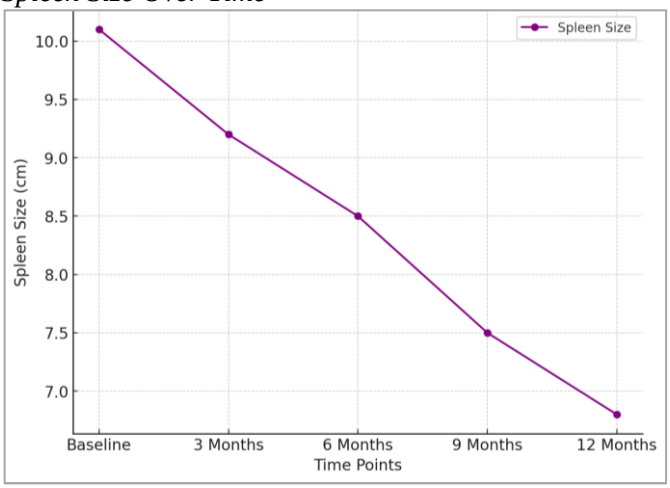
Table 5

Spleen and Liver Size Over Time

Time Point	Spleen Size (cm)	Liver Size (cm)
Baseline	10.1 ± 1.8	12.3 ± 1.5
3 Months	9.2 ± 1.5	11.5 ± 1.3
6 Months	8.5 ± 1.5	10.5 ± 1.2
9 Months	7.5 ± 1.3	9.8 ± 1.1
12 Months	6.8 ± 1.2	9.2 ± 1.0

Figure 5

Spleen Size Over Time



The reduction in spleen and liver size indicates a reversal of hypersplenism and hepatomegaly, both of which are common complications in TDT patients. These improvements are likely due to reduced transfusion dependence and improved hematological parameters.

Safety and Adverse Events

Mild adverse events were reported in 12% of patients, including constipation (6%), fatigue (3%), and dizziness (3%). Serious adverse events, such as thrombosis, were observed in two patients (4%), leading to temporary discontinuation of therapy. Liver and kidney function tests, including ALT, bilirubin, and creatinine levels, remained stable throughout the study, with no significant changes (**Table 2**).

Table 6

Adverse Events and Biochemical Safety Parameters

Adverse Event	Frequency (%)	Outcome
Constipation	6%	Resolved
Fatigue	3%	Resolved
Dizziness	3%	Resolved
Thrombosis	4%	Resolved with care

Table 7

Biochemical Safety Parameters Over Time

Biochemical Parameter	Baseline Value	6 Months	12 Months
ALT (IU/L)	32 ± 5	30 ± 4	29 ± 3
Bilirubin (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.2
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1

The safety profile of thalidomide was largely favorable, with adverse events being mild and manageable. Serious adverse events were rare and resolved with appropriate management, indicating that thalidomide is a well-tolerated therapeutic option in TDT patients.

DISCUSSION

The implications of this study are an exploration and evaluation of the impact of thalidomide for the treatment of transfusion-dependent β-thalassemia, particularly among patients who do not respond to hydroxyurea. These outcomes are consistent with and add to the data on the use of thalidomide to enhance the efficacy of hematological indicators, decrease reliance on transfusions, and prevent adverse outcomes in patients with chronic anemia and complications of transfusion-related comorbidities.

Elevation of Hb is a primary biomarker of therapeutic effects of thalidomide as revealed in the current investigation. Moving from to 6.2 ± 0.7 g/dL to 9.2 ± 0.5 g/dL at 12 months, the findings also demonstrate that the drug favours erythropoiesis. Such results are in line with earlier research studies, for instance, Lu et al. (2022) who observed an average of Hb rise by 2 g/dL in thalidomide employing patients and Ansari et al. (2022) who noted notable enhancements of Hb levels in the first half a year of treatment. The increase in Hb may be because thalidomide stimulates the fetal hemoglobin (HbF) synthesis that helps counter the α/β-globin disproportion common in β-thalassemia (Chen et al., 2021). Thalidomide induction of HbF suppresses IE and increases RBC production, which has been demonstrated in works of Yang et al. (2020) and Jiskani and Memon (2018).

This reduction of transfusion from this study also proves the applicability of thalidomide in clinics. Patients reduced their monthly transfusions from 2.5 ± 2.5 at baseline to 0.4 crosses after 1 year with 80% achieving transfusion independence. These results are in consonance with Chandra et al. (2021), who noted that of the patients who received thalidomide there was 65.9% complete transfundependent. Likewise, non-myeloablative transplantation showed improved transfusion independence in pediatric patients given thalidomide where almost half of these patients gained independence within the first year as supported by Li et al. (2021). Transfusion independence is not only more

effective for patients' quality of life but it also attenuates the probability of contracting conditions like iron overload, alloimmunization and transfusion transmitted infections (Vichinsky et al., 2014).

Serum ferritin, an indicator of iron excess, also reduced significantly in this study from a baseline of 2950 ± 450 ng/mL to 950 ± 250 ng/mL after 12 months. This reduction is well expected due to the reduction on demand for blood transfusion and improved iron utilization as a result of thalidomide induced erythropoiesis. The findings are in harmony with Nag et al., 2020 who described decreased serum ferritin in patients treated with thalidomide, as well as Yang et al., 2020 who noted enhanced iron metabolism in thalassemia intermedia patients under the therapy. The decrease of ferritin, which reduces potential iron induced complications as cardiovascular or hepatic disorder, is a benefit in the management of TDT patients (Algiraigri et al., 2017; Karimi et al., 2021).

Another notable achievement is decrease in serum LDH levels of lactate indicating decreased hemolysis, as corroborated by other researchers. The reduction from 240 ± 30 IU/L at baseline to 180 ± 20 IU/L at 12 months corresponds with the findings of Chen et al. (2021), as well as Yang et al. (2020) and reduced hemolytic activity attributed to thalidomide therapy. Lower LDH levels indicate that thalidomide not only facilitates the synthesis of red blood cells but also contributes to erythrocyte stabilization, which increases their lifespan and decreases the hemolysis that leads to anemia and other conditions in TDT (Chandra et al., 2021).

Based on the organ size measurements made in this study, there was a considerable decrease in the sizes of the spleen and liver over one year. Spleen size was reduced from 10.1 ± 1.8 cm to 6.8 ± 1.2 cm and liver size was reduced from 12.3 ± 1.5 cm to 9.2 ± 1.0 cm. In line with our study, Ramanan and Kelkar (2017) observed thalidomide ameliorated splenomegaly and hepatomegaly in cases of TN. Reduced organ size may be attributed to reduced need for transfusions and attainment of better haematological allosteric homeostasis as the work of hypersplenism and congestion in the anemic state is noticed in TDT patients.

In the present study, the safety profile of thalidomide was found to be generally positive as most side effects recorded were mild and easily containing. The most common adverse effects were constipation in 6% of patients, fatigue in 3% and dizziness in 3%. The efficacy of the therapy also seemed lower, with serious adverse events – thrombosis – reported in 4% of the patients, although these complications were resolved with adequate treatment. Our results are similar to the safety data presented by Ansari et al. (2022) and Nag et al. (2020), who also noted that thalidomide was observed to be safe when taken under medical supervision. In line with Chen et al. (2021) and Li et al. (2021), no significant changes in liver and kidney function tests were noted in the present study, indicating the safety of thalidomide.

The oral bioavailability, inexpensive nature and easy availability of thalidomide also make it particularly relevant to target TDT in LMICs because most of the other effective therapeutic interventions such as HSCT and gene therapy-based treatment are inaccessible in most of these settings. According to Karimi et al., (2021) and Jourdan et al., (2020) the high cost and some of the requirements needed to conduct the above treatments make it impossible to use them in most developing countries. On the other hand, for such regions, thalidomide presents a less expensive option capable of fulfilling the various needs of TDT patients.

The restrictions of the present work are to be noted, such as the absence of a control group and the study being conducted in a single institution. The findings are in agreement with the previous studies, however; further multicenter prospective, randomized trials are necessary to verify the benefits and safety of thalidomide in a variety of patient groups. In addition, more investigation should be conducted to investigate the HbF inducience effect of thalidomide and the identification of the molecular factors that could be helpful in the indication of the patients to the therapy.

Thus, this research proves the effectiveness and non-toxicity of thalidomide in the treatment for hydroxyurea-resistant TDT patients. The increase in hemoglobin levels, transfusion dependence, serum ferritin, and organ size, observed in the current study analysis, together with its safety profile, suggests that thalidomide may be useful in treating TDT. Intervening on the primary deficiencies of patients in low-resource settings, Thalidomide is a progressive step toward better management of β-thalassemia, and provides a new road map for the improvement of morbidity and mortality in the vulnerable patient populace. Further research should be directed to fine-tuning dosing regimens; evaluating QOL gains, and examining the drug in other fields of hemoglobinopathies.

CONCLUSION

This study has demonstrated the long-term efficacy and safety of thalidomide in the treatment of transfusion-dependent β-thalassemia patients resistant to hydroxyurea. The findings showed that thalidomide significantly improved hemoglobin levels, reduced the frequency of transfusions, decreased serum ferritin levels, and helped control hypersplenism and hepatomegaly. The overall safety profile was favorable, with manageable side effects and minimal severe complications. Considering its low cost and relative accessibility compared with other advanced therapies, thalidomide represents a potentially attractive option for

the treatment of β-thalassemia, especially in resource-limited settings. Larger multicenter, randomized controlled trials are necessary to confirm these results and optimize the treatment protocols.

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