ORIGINAL ARTICLE OPEN ACCESS

Follow-Up of Patients Undergoing Thalidomide Therapy for Transfusion-Dependent β-Thalassemia: A Single Thalassemia Center Cohort Study

Kiran Kanwal [1], Asma Akbar[1], Shakeel Ahmad Leghari[1], Irum Jabeen[1], Sonia Ilyas[1], Asmat Ullah[1], Zuhaib Hassan[1], Sajawal Shareef[1]

[1]*Department of Pediatrics, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan.*

ABSTRACT

Background: Thalassemia is a common inherited disorder globally. This study aimed to evaluate the long-term effects of thalidomide therapy in patients with transfusion-dependent β-Thalassemia (TDT).

Methods: This retrospective cohort study was done at the Thalassemia Center of Dera Ghazi Khan Teaching Hospital, Pakistan, from October 2019 to September 2024. A total of 500 children aged 1-15 years, diagnosed with TDT, and who had received thalidomide were analyzed. Non-probability, consecutive sampling technique was adopted. Necessary laboratory and clinical parameters were evaluated during the 5-year follow-up period. Data analysis was performed applying IBM-SPSS Statistics, version 26.0. Chi-square or Fisher's exact test was used to compare qualitative data, while ANOVA or independent sample t-tests were performed for quantitative data, considering $p<0.05$ as significant.

Results: Out of a total of 500 patients, 256 (51.2%) were female. The mean age was 8.25±2.19 years. The mean baseline Hb was 6.5±0.6 g/dl, rising to 8.5±0.5 g/dl at 6 months, and stabilizing at 8.6±0.4 g/dl at 1 year and 8.6±0.3 g/dl at 5 years ($p<0.001$). At baseline, all required monthly transfusions, with 307 (61.4%) becoming transfusion-independent by 6 months, 383 (76.6%) by 1 year, and 410 (82%) by 5 years ($p<0.001$). Chelation therapy was required for 453 (90.6%) patients at baseline, 308 (61.8%) at 6 months, 346 (69.2%) at 1 year, and 57 (11.4%) by 5 years ($p<0.001$). Significant liver, and spleen regression were noted by the end of the study period ($p<0.001$). All patients experienced abdominal distension, which resolved within 1 year, while 2 (0.4%) patients had cerebrovascular accidents.

Conclusion: Thalidomide therapy significantly improved hemoglobin levels, reduced transfusion and chelation needs, and led to organ size regression over five years in children with TDT, with minimal adverse effects, supporting its long-term efficacy and safety.

Keywords: β-Thalassemia, Chelation, Hemoglobin, Thalidomide, Transfusion.

Corresponding Author:
Dr. Kiran Kanwal,
Department of Pediatrics,
Allama Iqbal Teaching Hospital,
Dera Ghazi Khan, Pakistan.
Email: drzahraimran@gmail.com
ORCID: https://orcid.org/0009-0003-6058-2233
Doi: https://doi.org/10.36283/ziun-pjmd14-3/020

How to cite: Kanwal K, Akbar A, Leghari SA, Jabeen I, Ilyas S, Ullah A, Hassan Z, Shareef S Follow-Up of Patients Undergoing Thalidomide Therapy for Transfusion-Dependent β-Thalassemia: A Single Thalassemia Center Cohort Study. Pak J Med Dent. 2025 July ;14(3): 127-134. Doi: https://doi.org/10.36283/ziun-pjmd14-3/020.

Received: Thu, February 27, 2025 **Accepted:** Thu, July 10, 2025 **Published:** Mon, July 21, 2025

INTRODUCTION

Thalassemia is a common inherited disorder globally, particularly in Southeast Asia, the Mediterranean, and the Middle East[1]. In Pakistan, thalassemia is considered to be a significant public health problem, and estimates have shown that 5-7% of the population are carriers of the β-thalassemia trait[2]. In Pakistan, 5,000-9,000 children are born annually with thalassemia major, which leads to a significant burden on healthcare resources[2,3]. In a developing country like Pakistan, managing thalassemia is a challenge because of limited access to blood transfusions and chelation therapy, high treatment costs, and inadequate healthcare infrastructure.

In the last few decades, thalassemia care advanced significantly in the developed countries because of better transfusion and chelation protocols, but in developing countries, these treatments are still less accessible[4]. Blood transfusions are considered to be the cornerstone of thalassemia management but are related with risks like iron-overload, infections, and alloimmunization[5]. Chelation therapy is a well-established approach assisting in prevention of iron accumulation but is often costly and requires strict adherence[6].

Thalidomide was initially developed as a sedative and has gained interest in recent years for its potential role in reducing transfusion dependency in β-thalassemia by raising hemoglobin production[7]. Contemporary research in transfusion-dependent β-thalassemia (TDT) has demonstrated that thalidomide increases hemoglobin levels and reduces the need for transfusions[8,9]. These studies have evaluated relatively short-term outcomes, and long-term safety, especially related to its side effects like peripheral neuropathy and liver toxicity, has not been comprehensively explored yet.

Managing regular blood transfusions and iron chelation remains a challenge, often resulting in iron overload and subsequent organ damage[10]. Thalidomide is emerging as a potential alternative to reduce transfusion dependency[8,9]. While thalidomide has previously been explored as a therapeutic option in TDT, most available studies are either short-term, involve limited sample sizes, or lack long-term follow-up data in low-resource settings. The novelty of this study lies in its large sample size (n=500), extended follow-up duration of five years, and focus on a real-world pediatric population in a resource-constrained region of Pakistan. This is one of the few studies to document sustained hemoglobin stabilization, transfusion independence, and reduction in chelation burden over several years. This study also provides clinically relevant data on organ size regression and long-term safety outcomes, including rare adverse effects like cerebrovascular events. These findings contribute valuable regional evidence that supports the long-term integration of thalidomide into therapeutic protocols for TDT, especially in areas with limited access to curative options like bone marrow transplant. This study aimed to bridge this gap by assessing the safety and efficacy of thalidomide therapy in Pakistani patients with TDT over five years. The findings from this study may provide essential insights into the feasibility of thalidomide as a choice for its long-term use in TDT patients in Pakistan, contributing to improved thalassemia management in similar healthcare settings globally. At our thalassemia center, around 2000 thalassemia families are registered. The main aim of this study was to evaluate the long-term efficacy and safety of thalidomide therapy in patients with TDT in Pakistan.

METHODS

This retrospective cohort study was conducted at the thalassemia center of Dera Ghazi Khan Teaching Hospital, Pakistan, from October 2019 to September 2024. Approval from the Institutional Ethical Committee was sought (No.PM.U-L/008/56, dated: 18-2-2025). Being a retrospective study, it did not require prior approval as data was retrieved from the hospital record. Informed or written consents were also not required as no direct interactions were made with the patients for this study as data was gathered retrospectively from the hospital record. Non-probability, consecutive sampling technique was adopted. Data from hospital records of children of either gender, aged 1 to 15 years, diagnosed with TDT, receiving thalidomide therapy were analyzed. Exclusion criteria were children with severe comorbidities, including hepatitis B or central nervous system diseases. Data of patients with poor compliance to thalidomide therapy or irregular follow-up were not included. Thalidomide was not advised to children who were considered at high risk for venous

thromboembolism. Thalidomide was advised at a dose of 2-5 mg/kg/day based on clinical response[11,12].

Baseline characteristics like gender, age, weight, height, residential status, and previous history of blood transfusions were noted. Baseline Hb levels were recorded before starting thalidomide therapy, with subsequent measurements at 6 months, 1 year, and 5 years. The primary outcome was the stabilization or increase in Hb levels, targeting 8-9 g/dl. Transfusion independence was defined as the absence of transfusion requirement for at least one month (or longer), provided the patient maintained Hb ≥8 g/dL. Transfusion requirements were documented for each patient at baseline and throughout study intervals at 6 months, 1 year, and 5 years. Baseline liver and spleen sizes were noted based on clinical examination and ultrasound. These measurements were also evaluated by the end of the study period. Liver size was recorded as the distance in centimeters below the costal margin. Spleen size was measured similarly. Regression of the organ size was defined as a reduction in liver and spleen size compared to baseline. For patients with persistent hypersplenism, data on splenectomy was collected, including the timing and impact on transfusion frequency and Hb levels. Normal liver size for children aged 1–2 years is typically around 8.6 cm, at 2–4 years about 9.0 cm, at 4–6 years approximately 10.3 cm, at 6–8 years around 10.8 cm, and by 15 years between 6.5 and 8 cm. Normal spleen size in children aged 1–2 years ranges from 5.4 to 7.5 cm, in 4–6 years is 6.9 to 8.8 cm, 6–12 years from 7.0 to 10.9 cm, and in 12–15 years, the spleen usually measures 8.7 to 11.4 cm. At baseline, the chelation status of each patient was recorded, including the type (oral or IV), duration, and frequency of chelation therapy. All potential side effects of thalidomide such as abdominal pain, thromboembolic events, fatigue, or hepatotoxicity, were documented during the study period. Any serious adverse events leading to discontinuation of thalidomide were reported, including data on treatment modifications and patient outcomes. A special proforma was designed to record all relevant study information.

Data analysis was performed employing IBM-SPSS Statistics, version 26.0. Qualitative variables were shown as frequencies and percentages. Quantitative data were given representation in terms of mean and standard deviation. Categorical data were compared using a chi-square test. Analysis of variance or independent sample t-test (wherever applicable) was applied to compare quantitative data during various intervals. For all inferential statistics, $p<0.05$ was considered statistically significant.

RESULTS

Table 1: Baseline characteristics of patients (n=500)

Characteristics		Number (%)
Gender	**Male**	244 (48.8%)
	Female	256 (51.2%)
Age (years)	**1-5**	152 (30.4%)
	6-10	216 (43.2%)
	11-15	132 (26.4%)
Residence	**Rural**	310 (62.0%)
	Urban	190 (38.0%)

In a total of 500 patients, 244 (48.8%) were male, and 256 (51.2%) were female. The mean age was 8.25±2.19 years, ranging between 1-15 years. The mean at the time of diagnosis was 5.43±1.84 years. **Table 1** shows the baseline demographic characteristics of patients.

The mean baseline Hb was 6.5±0.6 g/dl, 8.5±0.5 g/dl at 6-months, 8.6±0.4 g/dl after 1-year, and 8.6±0.3 g/dl after 5-years ($p<0.001$), as shown in **Figure 1**.

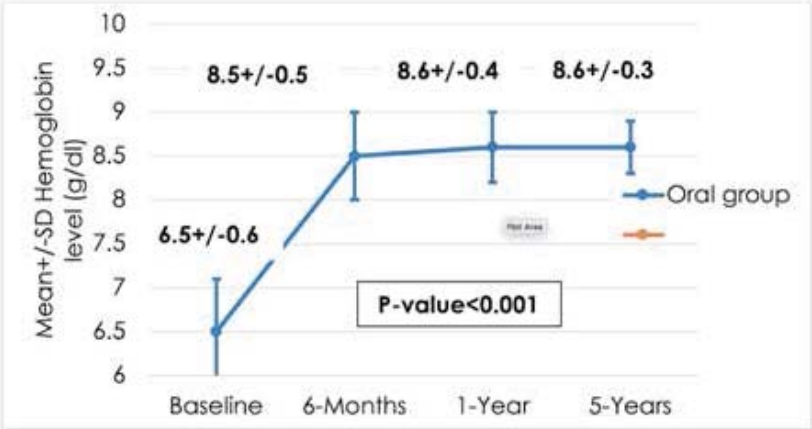

Figure 1: Comparison of Hemoglobin Levels During the Study Intervals

At baseline, all 500 patients (100%) required monthly transfusions. By 6 months, 307 (61.4%) patients were transfusion-independent. At 1 year, 383 (76.6%) patients became transfusion-independent, 56 (11.2%) required transfusions every 6-8 months, 41 (8.2%) needed transfusions 1-2 times per year, and 20 (4%) still needed monthly transfusions. By 5 years, 410 (82%) patients were transfusion-independent, 40 (8%) required transfusions every 6-8 months, 25 (5%) needed transfusions 1-2 times per year, and 25 (5%) still needed monthly transfusions ($p<0.001$). The details about the trends in requirement of transfusions through the study period are shown in **Figure 2.**

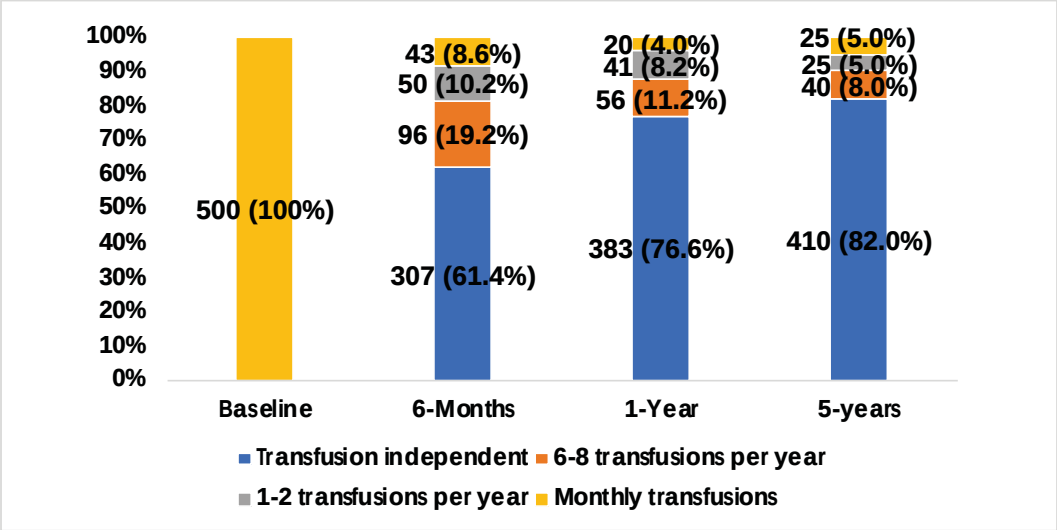

Figure 2: Transfusion Requirements Through the Study Period

At baseline, 453 (90.6%) patients required chelation therapy, 308 patients (61.8%) by 6 months**,** 346 (69.2%) at 1 year, and 57 patients (11.4%) at 5 years. The details about the need for chelation therapy during the study period are shown in **Figure 3**.

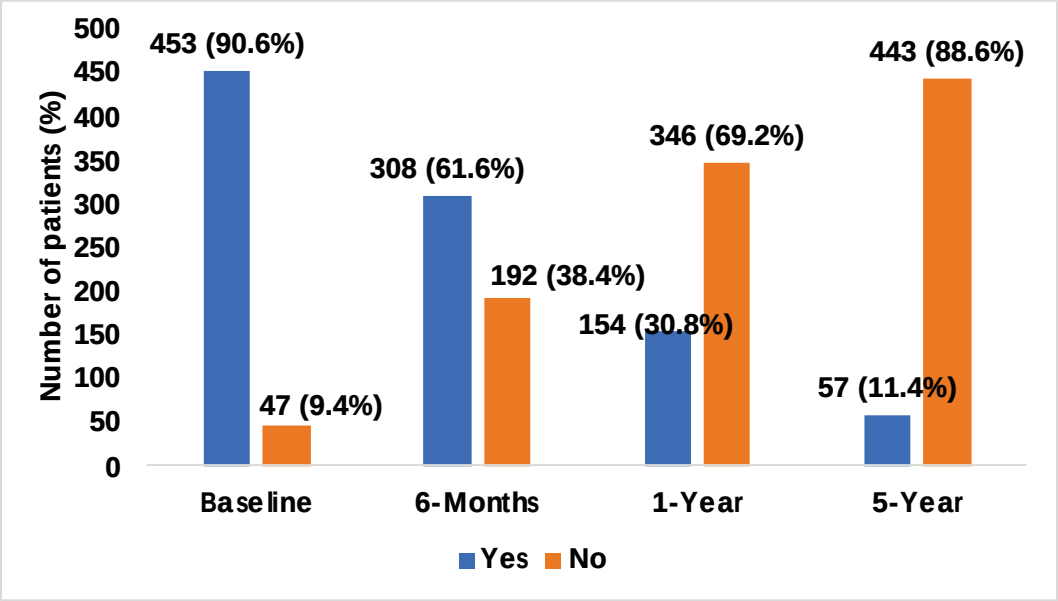

Figure 3: Need for Chelation Therapy During the Study Period (n=500)

Liver and spleen size regression below the costal margin at baseline and after 5 years showed significant differences (p<0.001) as depicted in **Figure 4.**

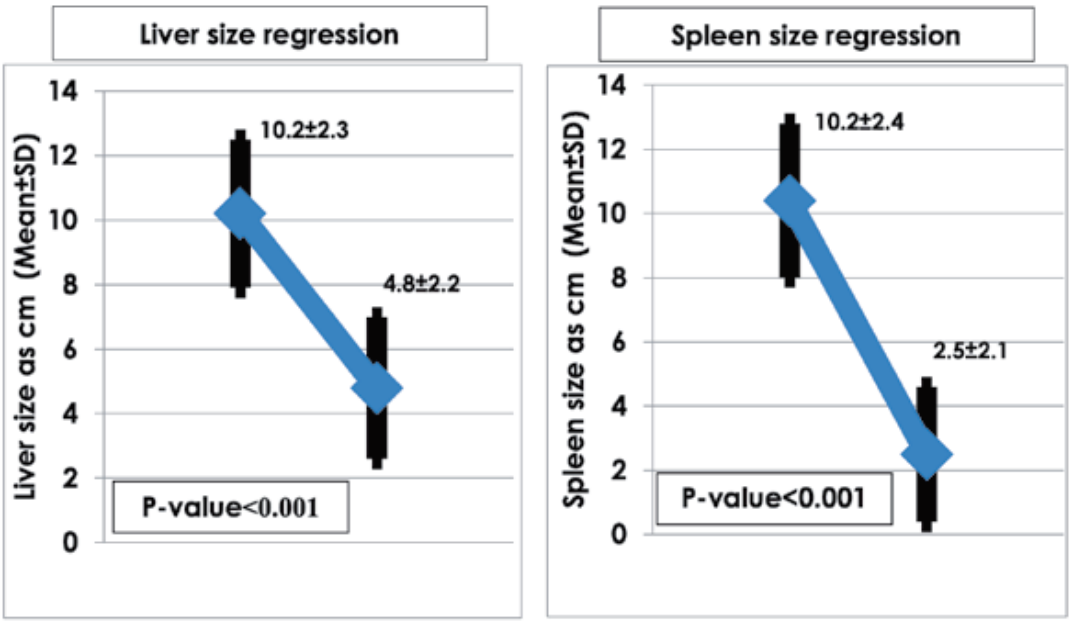

Figure 4: Liver and Spleen Size Regression at Baseline and After 5 Years

In terms of side effects, all 500 (100%) patients experienced abdominal distension, which resolved within 6 months to 1 year without requiring any additional treatment. Two patients experienced cerebrovascular accident, and it seemed to be dose dependent as both these patients had a relatively higher dose of Thalidomide (5mg/kg/day). Hepatitis was identified in 10 (2.0%) patients, which was initially thought to be due to Thalidomide, but it was noted to be due to hepatitis A upon further evaluation.

DISCUSSION

One of the key findings of this study was the marked improvement in hemoglobin levels over time. The mean baseline Hb level was 6.5±0.6 g/dl, which increased to 8.5±0.5 g/dl at 6 months and remained stable at 8.6±0.3 g/dl after 5 years (p<0.001). This is consistent with the results of another local study from KPK province of Pakistan, where thalidomide led to a significant increase in Hb levels in TDT patient's refractory to hydroxyurea[13]. Some others have also reported that patients treated with thalidomide achieved Hb levels of 9.90±1.37 g/dL after 9 months, demonstrating thalidomide's efficacy in improving Hb concentrations. The increase in Hb observed in this study can be attributed to thalidomide's potential to stimulate erythropoiesis and elevate HbF levels, as suggested by others, highlighting an increase in HbF after thalidomide therapy[14].

At baseline, all 500 patients required monthly transfusions, but after 6 months, 61.4% patients were transfusion-independent. By the 1-year mark, this number rose to 76.6%, and by 5 years, 82.0% patients were transfusion-independent (p<0.001). Local data have reported that 76.7% of patients on thalidomide achieved transfusion independence[13]. The transfusion reduction in this cohort may be due to the stabilization of Hb levels and improved erythropoiesis, as another study showed that 84% of patients became transfusion-independent after 48 months of thalidomide treatment[11]. However, the results of this study diverge from few others which reported a lower complete response rate of 54%, likely due to differences in dosage regimens, patient populations, or genetic factors such as β-globin mutations[15,16].

The reduction in the need for chelation therapy in this study was another significant outcome. At baseline, 90.6% patients required chelation therapy, but this number dropped to 61.8% by 6 months and to only 11.4% at 5 years. This is comparable to findings of another local study where thalidomide led to a reduction in ferritin levels and iron overload[16]. Thalidomide's ability to reduce transfusion frequency, thereby lowering iron accumulation, is likely responsible for the reduced need for chelation in this study. However, it is important to note that the present study did not assess serum ferritin levels directly, which could be a limitation in determining the full scope of thalidomide's effect on iron overload.

Liver and spleen size regression were also significant in this study, with liver size decreasing from 5.2±1.1 cm to 1.8±0.7 cm below the costal margin after 5 years (p<0.001), and spleen size decreasing from 9.5±2.0 cm to 4.2±1.3 cm (p<0.001). These findings seem consistent with the contemporary literature that noted a reduction in spleen size with thalidomide therapy[17]. The regression of organomegaly in this study could be linked to decreased hemolysis and splenic sequestration, as reduced transfusion needs lessen the burden on the liver and spleen to clear damaged red blood cells.

Adverse events in this study were minimal, with all patients experiencing abdominal distension that resolved within 6 months to 1 year. Two patients developed cerebrovascular accidents, which seemed to be dose-dependent. Similar safety profiles have been stated in the published literature where most side effects were mild and manageable, though serious events such as cerebrovascular accidents were reported at higher doses[11,14]. The minimal adverse effects seen in this study can be attributed to the careful dose management of thalidomide, as doses were gradually increased and maintained at a tolerable level.

The clinical implications of this study are significant. Thalidomide offers a viable long-term treatment option for patients with TDT, particularly in resource-limited settings where access to regular transfusions and chelation therapy may be challenging[18,19]. The ability of thalidomide to reduce transfusion frequency and chelation requirements can greatly improve the quality of life for patients and reduce the healthcare burden associated with managing TDT[20-22]. The minimal side effects observed in this study suggest that thalidomide is a well-tolerated therapy, although careful monitoring for serious events, particularly at higher doses, is essential[23-25].

The limitations of the study include its retrospective design, which inherently limits the ability to establish causality and introduces the potential for missing data. This study did not assess important biochemical markers such as serum ferritin levels due to missing data at various intervals, which would have provided a clearer understanding of thalidomide's impact on iron overload. Genetic factors influencing treatment response were not evaluated, which could explain the variation in outcomes compared to other studies. Further multicenter, prospective studies are needed to confirm the present findings and address these limitations.

CONCLUSION

The study demonstrated the long-term efficacy and safety of thalidomide in managing TDT. The significant improvements in Hb levels, reductions in transfusion dependency, and decreases in chelation requirements suggest that thalidomide could be an essential therapeutic option for TDT patients. Future studies should explore the genetic factors that influence response to thalidomide and further evaluate its safety profile in larger, more diverse patient populations.

ACKNOWLEDGMENT
None

FUNDING
None

CONFLICT OF INTEREST
None

ETHICAL APPROVAL
This retrospective cohort study was conducted at the thalassemia center of Dera Ghazi Khan Teaching Hospital, Pakistan, from October 2019 to September 2024. Approval from the Institutional Ethical Committee was sought (No.PM.U-L/008/56, dated: 18-2-2025).

AUTHORS' CONTRIBUTIONS
All other Authors contributed equally as per IMCJE. All authors agreed to be accountable for all aspects of the research.

REFERENCES
1. Tuo Y, Li Y, Li Y, Ma J, Yang X, Wu S, et al Global, regional, and national burden of thalassemia, 1990-2021: a systematic analysis for the global burden of disease study 2021. E Clinical Medicine. 2024;72:102619. doi: 10.1016/j.eclinm.2024.102619
2. Khaliq S. Thalassemia in Pakistan. Hemoglobin. 2022;46(1):12-14. doi: 10.1080/03630269.2022.2059670
3. Ahmed S, Saleem M, Modell B, Petrou M. Screening extended families for genetic hemoglobin disorders in Pakistan. N Engl J Med. 2002;347(15):1162-8. doi: 10.1056/NEJMsa013234
4. Farmakis D, Porter J, Taher A, Domenica CM, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022;6(8):e732. doi: 10.1097/HS9.0000000000000732
5. Patterson S, Singleton A, Branscomb J, Nsonwu V, Spratling R. Transfusion Complications in Thalassemia: Patient Knowledge and Perspectives. Front Med (Lausanne). 2022;9:772886. doi: 10.3389/fmed.2022.772886
6. Reddy PS, Locke M, Badawy SM. A systematic review of adherence to iron chelation therapy among children and adolescents with thalassemia. Ann Med. 2022;54(1):326-342. doi: 10.1080/07853890.2022.2028894
7. Rehman W, Arfons LM, Lazarus HM. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. Ther Adv Hematol. 2011;2(5):291-308. doi: 10.1177/2040620711413165
8. Karim A, Akhter S, Jamal CY. Transfusion-dependent b-Thalassemia Major Bangladeshi Child Treated Successfully with Combination of Hydroxyurea and LowDose Thalidomide : A Case Report. Bangladesh J Child Health. 2023;47(2):117-120. Available from:https://www.banglajol.info/index.php/BJCH/article/view/77663/51144
9. Che J, Luo T, Huang L, Lu Q, Yan D, Meng Y, et al. Magnetic Resonance Imaging Quantification of the Liver Iron Burden and Volume Changes Following Treatment With Thalidomide in Patients With Transfusion-Dependent ß-Thalassemia. Front Pharmacol. 2022;13:810668. doi: 10.3389/fphar.2022.810668
10. Shah S, Farooq N, Basharat A, Shah M, Mukhtiar S, Farhad S. Frequency of iron overload complications in beta thalassemia major patients. J Postgrad Med Inst. 2019;33(1):30-3.
11. Zhu W, He Y, Huang M, Fu S, Liu Z, Wang X, et al. Long-Term Follow-Up of Patients Undergoing Thalidomide Therapy for Transfusion-Dependent β-Thalassaemia: A Single-Center Experience. Int J Gen Med. 2024;17:1729-1738. doi: 10.2147/IJGM.S462991
12. Yassin AK. Promising Response to Thalidomide in Symptomatic β-Thalassemia. Indian J Hematol Blood Transfus. 2020;36(2):337-341. doi: 10.1007/s12288-019-01231-5
13. Ali Z, Ismail M, Rehman IU, Rani GF, Ali M, Khan MTM. Long-term clinical efficacy and safety of thalidomide in patients with transfusion-dependent β-thalassemia: results from Thal-Thalido study. Sci Rep. 2023 ;13(1):13592. doi: 10.1038/s41598-023-40849-4
14. Chandra J, Parakh N, Sidharth, Singh N, Sharma S, Goel M, et al. Efficacy and Safety of Thalidomide in Patients With Transfusion-Dependent Thalassemia. Indian Pediatr. 2021;58(7):611-616.
15. Lu Y, Wei Z, Yang G, Lai Y, Liu R. Investigating the Efficacy and Safety of Thalidomide for Treating Patients With ß-Thalassemia: A Meta-Analysis. Front Pharmacol. 2022;12:814302. doi: 10.3389/fphar.2021.814302
16. Idrees M, Khan MTM, Bawazir W, Hazzazi MS, Kabrah SM, Altayar MA, et al. Safety and efficacy of low-dose thalidomide in patients with transfusion dependent thalassemia: a clinico-hematological assessment. J Populat Therap Clin Pharmacol. 2023;30(17):1344-1353. doi: 10.53555/jptcp.v30i17.2709
17. Yang WJ, Kang QP, Zhou Q, Lin T, Gong XM, Huang CJ, et al. Clinical efficacy of thalidomide for various genotypes of beta thalassemia. BMC Med Genomics. 2024;17(1):191. doi: 10.1186/s12920-024-01963-y
18. Mehta P, Yadav N, Soni P, Thekuddan SF, Singh R, Khushoo V, et al. Experience with Low Dose Thalidomide in Transfusion Dependent Beta Thalassaemia in a Resource Limited Setting. Blood. 2019;134(Supp_1):963. doi: 10.1182/blood-2019-131682
19. Chen JM, Zhu WJ, Liu J, Wang GZ, Chen XQ, Tan Y, et al. Safety and efficacy of thalidomide in patients with transfusion-dependent β-thalassemia: a randomized clinical trial. Signal Transduct Target Ther. 2021;6(1):405. doi: 10.1038/s41392-021-00811-0
20. Tahira A, Subhan Z, Nabi M, Ain NU, Ali W. Long Term Thalidomide therapy's Efficacy and Safety in

Transfusion-Dependent Beta Thalassemia Major Patients: A Systematic Review. Khyber Med Uni J. 2024;16(3). doi:10.35845/kmuj.2024.23705
21. Bhattacharjee S, Ghosh S, Shaw J, Bhattacharjee S, Bhattacharyya M. Thalidomide and Hydroxyurea in Transfusion-Dependent Thalassemia: Efficacy, Safety Profile and Impact on Quality of Life. Hemoglobin. 2024;48(3):161-168. doi: 10.1080/03630269.2024.2386076
22. Biswas S, Smrity SZ, Bhuia MS, Sonia FA, Aktar MA, Chowdhury R, et al Beta-Thalassemia: A Pharmacological Drug-Based Treatment. Drugs Drug Candidates. 2024;3(1):126-147. doi: 10.3390/ddc3010008
23. Peng X, Lin ZW, Zhang M, Yao JY, Zhao JZ, Hu PJ, et al. The efficacy and safety of thalidomide in the treatment of refractory Crohn's disease in adults: a double-center, double-blind, randomized-controlled trial. Gastroenterol Rep (Oxf). 2022;10:-goac052. doi: 10.1093/gastro/goac052
24. Yu Y, Li Y, Cui R, Yan Y, Li F, Chen Y, et al. Thalidomide-based regimen shows promising efficacy in large granular lymphocytic leukemia: a multicenter phase II study. Signal Transduct Target Ther. 2025;10(1):85. doi: 10.1038/s41392-025-02164-4
25. Wimmelbücker L, Kar A. A history of thalidomide in India. Med Hist. 2023;67(3):228-246. doi: 10.1017/mdh.2023.27