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SAFETY AND EFFICACY OF LOW-DOSE THALIDOMIDE IN PATIENTS WITH TRANSFUSION DEPENDENT THALASSEMIA: A CLINICO-HEMATOLOGICAL ASSESSMENT

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Abstract

Background: β-thalassemia is an autosomal recessive hereditary hemoglobin production disorder characterized by abnormal hemoglobin synthesis. The efficient and safe therapies for transfusion-dependent β-thalassemia (TDT) patients are desperately required to minimize the requirement for blood transfusion.

Objective: To establish the safety and efficacy of low-dose thalidomide in TDT patients.

Methodology: The retrospective cohort study was conducted in Khyber Medical University, Peshawar and Blood Diseases Clinic, Peshawar to investigate the safety and efficacy of low-dose

thalidomide therapy in TDT patients. Samples were collected from the diagnosed cases of TDT patients whose ages were ≥3 years and were on thalidomide treatment for a period of ≥6 months. Complete blood count CBC was performed on Sysmex XP-100, Japan and biochemical tests were performed on Cobas 6000 analyzer series. Comprehensive patients' demographics, clinical history and prognosis data were recorded and analyzed using the SPPS 27.

Results: The patient characteristics, biochemical parameters and hematological response were assessed and statistically tested for 384 TDT patients using low-dose thalidomide therapy. Applying the criteria for the Hb level achievement, we marked the significant results (<0.001) for Excellent, Good, and Partial responders that were 184 (47.9%), 96 (25%), and 60 (15.6%), respectively. The common side effects observed with the drug included abdominal discomfort, nausea, vomiting, headache, constipation, dizziness, fatigue, anxiety, repeated infections, and skin rash, that were controlled with symptomatic treatment and/or dose adjustment.

Conclusion: Collectively, thalidomide is safe and effective in increasing Hb levels thus reducing the requirements of blood transfusion in TDT patients. Future clinical trials are suggested to strengthen the efficacy and safety of low-dose thalidomide and to establish clinical guidelines for its rational use in TDT patients.

Key words: β-Thalassemia, prevalence, thalidomide, efficacy, safety

1. Introduction

β-thalassemia is hereditary hemoglobin (Hb) production disorder characterized by abnormal Hb synthesis that results in shorter red blood cell (RBC) survival due to hemolysis and the early death of RBC progenitors in the bone marrow [1]. The hall mark of a disease in this syndrome is ineffective erythropoiesis, chronic hemolysis, anemia and clinical consequences secondary to iron overload after regular multiple transfusions [2, 3]. When β-thalassemia is not treated in the early stages, it results in hepatosplenomegaly and cardiac failure due to persistent severe anemia and bone abnormalities associated with expansion of bone marrow [4, 5]. Clinically, β-thalassemia is classified based on the blood transfusion requirement as transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) based on phenotypic severity due to an imbalance in the α and β globin ratio, which can result from a variety of homozygous and heterozygous state mutations.

The prevalence of β-thalassemia and its mutations are highly geographical and ethnicity dependent. The highest rates are reported from the middle east and Mediterranean region and some Asian countries, with some communities reporting rates of up to 10% [6]. Carriers of the mutation may be asymptomatic or have mild anemia in these places, but those with β-thalassemia major, requires regular blood transfusions and other medical measures to manage their ailment. In Asia, the main countries such as India, Pakistan, and Thailand have a higher prevalence of mutations among their TDT patients. In India, the carrier rate for β-thalassemia is between 3 and 17 percent, with an incidence of β-thalassemia major of about 1 in 10,000 live births [7]. The incidence of transfusion dependent β-thalassemia in Pakistan is estimated to be around 1 in 5,000 live births. This is higher than the rate of 1 in 100,000 live births worldwide [8].

Thalidomide, being a synthetic glutamic acid derivative drug has anti angiogenic and immunomodulatory effects [9]. Nowadays, the drug is used in multiple neoplastic disorders including malignant melanoma and multiple myeloma. Thalidomide is reported to enhance the production of fetal hemoglobin and also reported to enhance the expression of EKLF gene, GATA-1 gene, and gamma globin gene [10]. Research work is being done to establish the efficacy of thalidomide in the treatment of thalassemia [11-15]. Still, more work is required in this regard as current research is very scanty [16]. Recently, some large studies are being conducted which will establish the guidelines for the use of drug. However, the effects of drug in thalassemia patients in Pakistan are not yet fully explored.

In the current study, we aim to investigate the efficacy of low-dose Thalidomide therapy and to assess its safety in the study population by observing major ADRs, so, to explore clinical evidence for the rational practice of thalidomide in TDT patients.

2. Materials and Methods

The retrospective cohort study was conducted in the Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar and Blood Diseases Clinic, Peshawar. A total of 384 patients were assessed for eligibility at Blood Diseases Clinic, Peshawar. Study duration was between September 2021 and August 2022.

Sample selection

All subjects fulfilling the inclusion and exclusion criteria were selected for the blood sample collection in the study. Diagnosed cases of TDT, both genders with ≥3 years of age, taking thalidomide for ≥6 months were recruited in the research. Cases having active systemic or metabolic co-morbidities or those lacking essential clinical details were excluded from the study. Non-compliant patients' data were also excluded from the final data analysis.

Data Collection Procedure

The initial requirements for sample collection are presented in a flowchart as **Figure-1**.

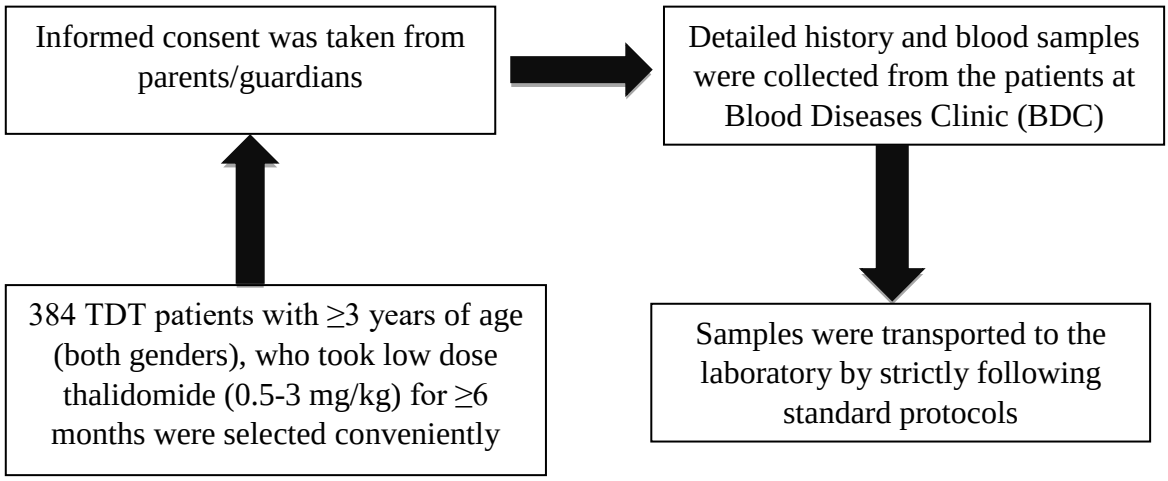

Figure 1: Graphical Flowchart for the Methodology

Clinico-hematological Assessment

A proforma was designed that had demographic and clinico-hematological data of the study participants. For each participant, the proforma was filled in by a trained physician after doing a complete clinical examination of each participant. The history of blood transfusion and treatment with low-dose thalidomide was recorded in detail. TDT patients receiving thalidomide, remaining transfusion independent in the last two months and maintaining an Hb levels of ≥9.0g/dl were labeled as Excellent Responders (ExR), patients maintaining an Hb levels of 7.0 to 8.9g/dl were labeled as Good Responders (GR), patients maintaining an Hb levels of 6.0 to 6.9g/dl as Partial Responders (PR) and those showing no significant improvement in Hb levels as Non-Responders (NR). Data was collected and analyzed using the SPPS 27.

Sample Collection

A volume of 5 ml venous blood was drawn. Two ml blood was collected in an EDTA purple-top tube, and the remaining 3ml was stored in a yellow-top Gel tube for biochemical tests. CBC was performed with automated hematology analyzer (Sysmex XP-100, Japan) and biochemical tests were performed on Cobas 6000 analyzer series (Roche Diagnostic Systems, Mannheim, Germany).

3. Results

Patient Characteristics

The clinical presentation of β-thalassemia depends on the severity of the disease and the age at which it first appears. The median age of cases was 5 years with a range of 3-24. About 62% cases were male and 38% were female. The median weight was 17.5 kg with a range of 8-65. The mean thalidomide dosage administered was 2.1±0.6 mg/kg/day with median total thalidomide treatment duration of 19.2 months and range of 6-58. The median age at first transfusion was 6 months, range being 1-108. As far as the last transfusion was concerned at the time of assessment, it was in the range of 2-63 months with a median value of 14 months as shown in **Table 1.**

Table 1: Patient characteristics

Characteristics		Values	Calculation Mode
Age (years)		5 (3, 24)	median (range)
Gender	Male	238 (62%)	n (%)
	Female	146 (38%)	
Weight (kg)		17.5 (8, 65)	median (range)
Thalidomide Dosage (mg/kg/day)		2.1 (±0.6)	mean (SD)
Thalidomide Treatment Duration (months)		19.2 (6, 58)	median (range)
Age at 1st Transfusion (months)		6 (1, 108)	median (range)
Last Transfusion Status (months)		14 (2, 63)	median (range)

Biochemical Parameters

The plasma levels of Bilirubin, Alanine transaminase ALT, Creatinine, and Uric Acid were 1.1 (0.2, 7.0), 28.0 (0.4, 156), 0.40 (0.1, 0.8), and 3.2 (2.1, 30.6), respectively. The observed median level of Lactate dehydrogenase LDH was 3.2 (2.1, 30.6), for Random blood sugar RBS 87 (74, 97), while observed Thyroid stimulating hormone TSH was 2.5 (0.1, 6.1) in the selected TDT patient group treated with low dose thalidomide. The median values with a minimum and maximum range of these parameters are presented in **Table 2**. Some of these parameters showed an extended range of values that reflect the diversity in patient's clinical characteristics and the disease severity.

Table 2: Observed biochemical parameters in the selected patients.

Parameters	Median (range)	Normal Range
Bilirubin	1.1 (0.2, 7.0)	0.1-1.2 (mg/dL)
ALT	28.0 (0.4, 156.0)	4-36 (U/L)
Creatinine	0.40 (0.1, 0.8)	0.7-1.3 (mg/dL)
Uric Acid	3.2 (2.1, 30.6)	3.5-7.2 (mg/dL)
LDH	213.5 (106, 568)	105-333 (IU/L)
RBS	87 (74, 97)	< 126 (mg/dL)
TSH	2.5 (0.1, 6.1)	0.5-5.0 (mIU/L)

Hematological Response

The observed median value of Hb in the selected TDT patients was 8.7 with an extended range of 3.4-17.2 g/dl. WBC, RBC, MCV, HCT and platelets count were 7.4 (1.2-147), 3.4 (1.2-8.1), 77.6 (51-104), 27.1 (9.5-57.3), and 296 (46-953), respectively as shown in **Table 3.**

Table 3: Observed hematological response of the study patients.

Parameters	Median (range)	Normal Range
Hb	8.7 (3.4, 17.2)	M: 13.8-17.2 (g/dL) F: 12.1-15.1 (g/dL)
WBC	7.4 (1.2, 147.0)	4.5-11.0 ($\times 10^9$ per L)
RBC	3.4 (1.2, 8.1)	M: 4.0-5.9 ($\times 10^{12}$ per L) F: 3.8-5.2 ($\times 10^{12}$ per L)
MCV	77.6 (51, 104)	80-100 (Femtoliter fl)
MCH	25 (18, 36)	27-31 picograms/cell
MCHC	32 (27, 40)	32-36 (g/dL)
HCT	27.1 (9.5, 57.3)	M: 41-50 (%) F: 36-48 (%)
PLT	296 (46, 953)	150-350 ($\times 10^3$)

(Hb- Hemoglobin, WBC- White blood cells, RBC- Red blood cells, MCV- Mean corpuscular volume, MCH- Mean corpuscular hemoglobin, MCHC- Mean corpuscular hemoglobin concentration, HCT- Hematocrit, PLT- Platelets)

Thalidomide Phenotypic Response- Drug Efficacy

Observing our selected criteria based on the Hb level achievement, we marked the significant results for Excellent, Good, and Partial responders that were 184 (47.9%), 96 (25%), and 60 (15.6%) respectively, while 44 (11.5%) patients were found to have been non-responders. Phenotypic description for thalidomide responses in study population are shown in **Figure 2**.

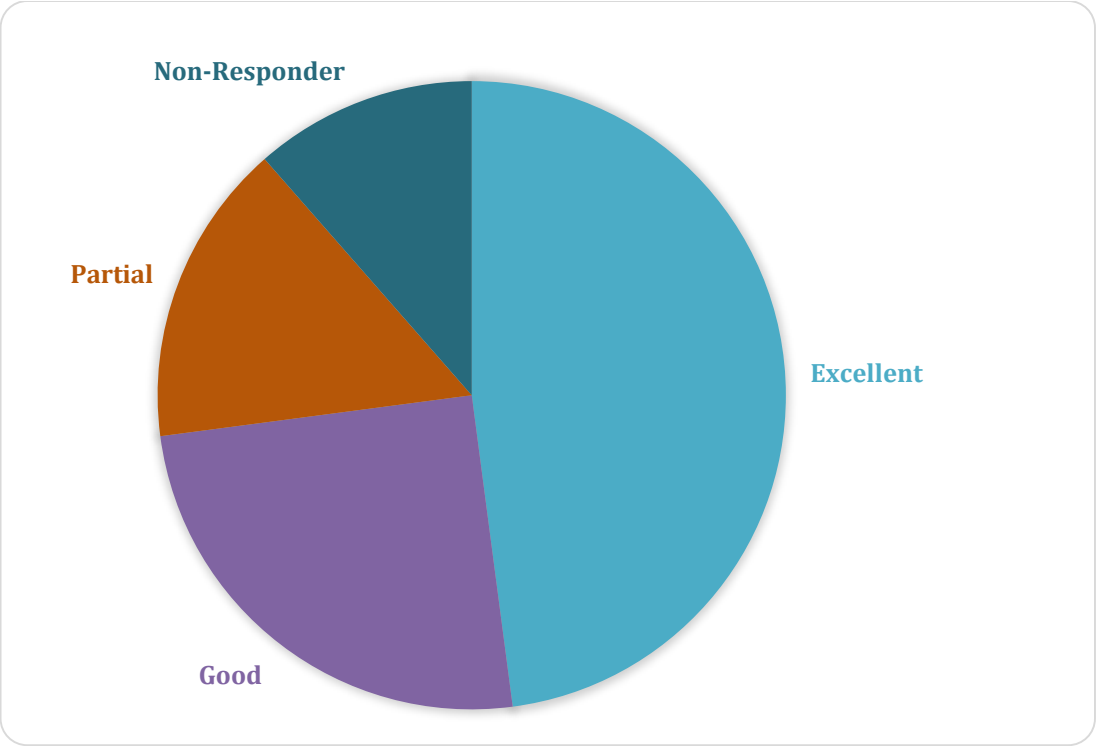

Figure 2: Low-dose Thalidomide Response in the Study Population.

Response Correlation with Patient Characteristics

The possible correlation of patient's characteristics with TDT patients treated with low dose thalidomide, for comparing mean, we applied ANOVA, while for comparing median (skewed data) and having more than 2 samples, Kruskal-Wallis Test is applied in this study. Results demonstrated that thalidomide dosage and duration of the last blood transfusion both showed statistically significant correlation (< 0.001), while the thalidomide treatment duration showed a closer but non-

significant value of 0.079 as presented in **Table 4**. Age, gender, weight (kg), and age at 1st transfusion remained statistically non-significant in the current study.

Table 4: Significance level of patient characteristics

Characteristics	*P* value
Age (years)	0.081
Gender	0.911
Weight (kg)	0.087
Thalidomide Dosage (mg/kg/day)	< 0.001
Thalidomide Treatment Duration (months)	0.079
Age at 1st Transfusion (months)	0.655
Last Transfusion Status (months)	< 0.001

Response Correlation with Hematological and Biochemical Parameters

Considering the significance of hematological and biochemical parameters in the clinical presentation of TDT patients, its statistical correlation has been investigated in this study. Results showed that in hematological parameters Hb, RBC, and HCT correlation is highly significant with the *p*-values of < 0.001, while MCV is statistically significant with the value of 0.002.

Among biochemical parameters, creatinine and LDH were highly significant (< 0.001), while bilirubin, ALT, uric Acid, RBS, and TSH showed statistically non-significant *p*-values. The values are tabulated in **Table 5**.

Table 5: Correlation of biochemical and hematological response in TDT patients

	Parameters	*P* value
Hematological	Hb	< 0.001
	WBC	0.287
	RBC	< 0.001
	MCV	0.002
	MCH	0.08
	MCHC	0.023
	HCT	< 0.001
	PLT	0.008
Biochemical	Bilirubin	0.571
	ALT	0.656
	Creatinine	< 0.001
	Uric Acid	0.201
	LDH	< 0.001
	RBS	0.272
	TSH	0.827

Thalidomide Safety

Drug safety is an essential aspect of medical therapy that can play a major role in deciding which drug should be given to a patient. In the current study common side effects observed from the drug were abdominal discomfort (53, 13.8%), nausea (48, 12.5%), vomiting (25, 6.5%), headache (22, 5.7%), constipation (14, 3.6%), dizziness (19, 4.9%), fatigue (27, 7.0%), anxiety (22, 5.7%), repeated infections (12, 3.1%), and skin rash (19, 4.9%), as presented in **Figure 3**.

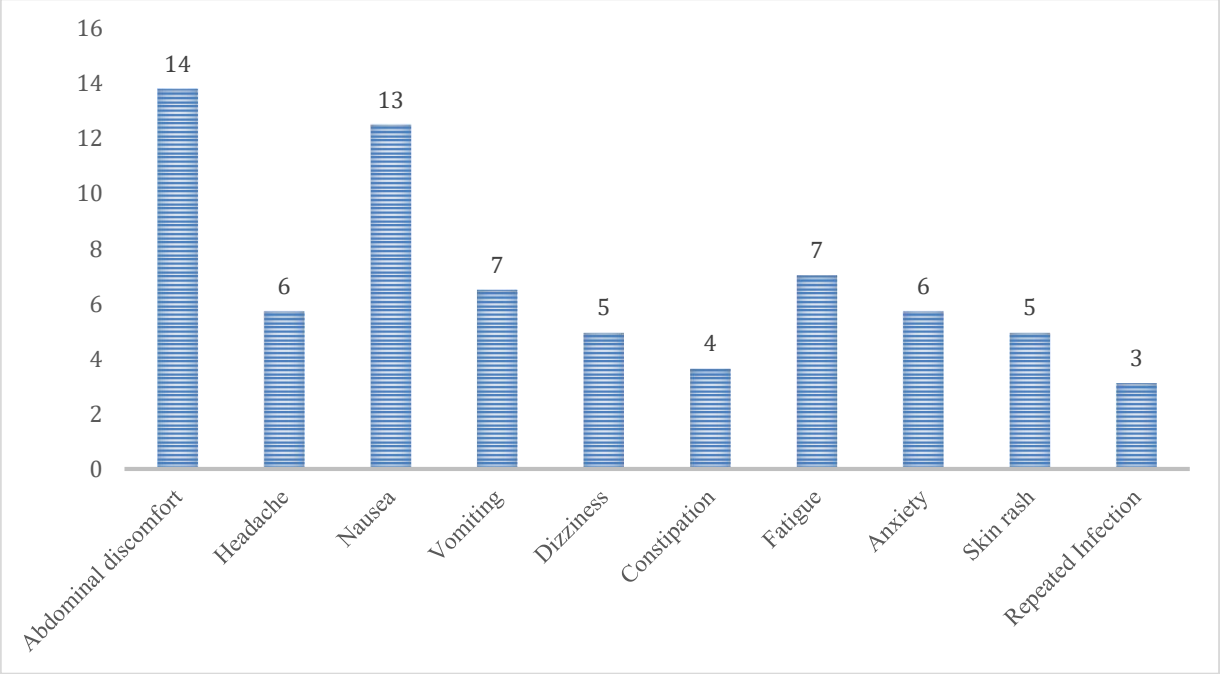

Figure 3: Observed Side-Effects and Suspected ADRs from the Thalidomide Treatment (values are in percentages)

4. Discussion

Transfusion-dependent β-thalassemia is the most severe form of the disease and requires round-the-clock care and monitoring from a team of medical professionals at a specialized facility. There has been a substantial improvement in patient prognosis because of advances in TDT diagnosis and therapy over the past few decades, but the disease is still difficult to manage.

Achieving and then maintaining a high Hb levels is still a major difficulty for β-thalassemia patients, despite the therapeutic breakthroughs made in recent years. Novel, efficient, and safe therapies for β-thalassemia are thus desperately required. Current clinical data observed a significant increase in physician interest in fetal hemoglobin (HbF) inducers, and thalidomide has been touted as a promising medication for the treatment of β-Thalassemia. Thalidomide was taken off the market due to its teratogenic effects, despite being first utilized to decrease vomiting during pregnancy. It has been utilized once again to treat autoimmune illnesses as an immunomodulatory and anti-angiogenic medication. Few retrospective investigations have revealed that thalidomide, a potent HbF inducer, may help individuals with β-thalassemia by improving their clinical symptoms and quality of life [14, 15, 17].

Strict monitoring of biochemical and hematologic parameters in thalassemia patients helps to determine the need for blood transfusions and related supplementation. Considering the significance of hematological and biochemical parameters in the clinical presentation of TDT patients, its statistic correlation has been investigated in this study. Our findings suggested that in hematological parameters Hb, RBC, and HCT correlation is highly significant with the p-values of < 0.001, while MCV is statistically significant with the value of 0.002. Among biochemical parameters, creatinine and LDH were highly significant (< 0.001), while bilirubin, ALT, Uric acid, RBS, and TSH showed statistically non-significant p-values.

When first used as a tranquilizer, thalidomide was shown to be teratogenic because of its ability to bind to the ubiquitin E3 ligase cereblon [18], resulting in the destruction of the transcription factor SALL4 [19]. By causing the degradation of C2H2 zinc finger-containing transcription factors Ikaros and Aiolos, thalidomide and its derivatives have been utilized to treat a variety of different conditions, including systemic sclerosis, triple-negative breast cancer, multiple myeloma [20-22]. Current clinical data indicates a significant increase in physician's interest in HbF inducers and thalidomide has been appraised as a promising drug for the treatment of β-thalassemia. Many clinical studies have reported thalidomide use, effectiveness, and safety in β-thalassemia patients

from the various communities of the World [12, 14, 23-29]. Retrospective investigations have revealed that thalidomide, a potent HbF inducer, may help individuals with β-thalassemia by improving their clinical symptoms and quality of life [12, 13, 27]. A multicenter randomized, phase-II clinical trial by Chen et al., [12] investigating safety and efficacy of thalidomide in TDT patients demonstrated a substantial rise in Hb concentrations and a decline in packed cell units transfusion in individuals using Thalidomide. After 48 weeks of treatment with thalidomide, the Hb of cases was maintained at >10.5 g/dl without red cell transfusion and no serious side effects (grades III-IV ADRs) were identified.

Observing the selected criteria based on the Hb level achievement, we marked the significant results (<0.001) for Excellent, Good, and Partial responder that were 184 (47.9%), 96 (25%), and 60 (15.6%), respectively. Spearman's rho correlations showed that thalidomide therapy response is significant (p=0.03) in the selected study population of Pakistani community.

Although various adverse events related to nerve damage, cardiovascular system and liver damage have been reported in thalidomide recipients. Several research studies supported the safety profile of Thalidomide in β-thalassemia patients [11, 12, 15, 28, 30]. Despite some very common ADRs related to the use of thalidomide, they were all easily managed by monitoring and dose adjustment. None of these research studies indicated grade-III or IV ADRs during its treatment that further supports thalidomide safety. Thalidomide therapy is safe for TDT patients when used in lower doses as we observed a very few suspected ADRs. The common side effects observed from the drug included abdominal discomfort (13.8%), nausea (12.5%), vomiting (6.5%), headache (5.7%), constipation (3.6%), dizziness (4.9%), fatigue (7.0%), anxiety (5.7%), repeated infections (3.1%), and skin rash (4.9%), that were subsided with symptomatic treatment and/or dose adjustment. Overall, thalidomide's side effects were manageable, suggesting that it has potential to preferably treat TDT patients. Our results are according to the recent published meta-analysis by Lu et al., [15] reporting that thalidomide treatment is relatively safe and obviously effective to decline the blood transfusions and improve Hb level in β-thalassemia patients, confirming thalidomide role as a potential HbF inducer.

5. Conclusion

Our findings suggested the significant response of low-dose thalidomide in TDT patients with a high rate of respondents falling in the excellent or good responders' category that clearly indicates its efficacy in TDT patients. Overall, thalidomide's side effects were manageable suggesting that low-dose of Thalidomide has potential to preferably treat TDTs with an acceptable range of safety profile. This study will attract clinicians towards the efficacy and safety of thalidomide and set a platform to encourage mechanistic approach for pharmacokinetics and pharmacodynamics of thalidomide in TDT.

Acknowledgement

We are grateful to the consultants of Blood Diseases Clinic and Khyber Medical College/ Khyber Teaching Hospital, Peshawar for granting access to the clinical data, blood sampling of the patients through informed consent and provision of diagnostic and research facilities.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical statement

After review of the study protocol, it was approved by the Institutional Research and Ethical Review Board (IREB) of Khyber Medical University, Peshawar, Pakistan.

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