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Original Article

Efficacy and Safety of Low Dose Thalidomide in Transfusion Dependent Thalassemia Patients: A Preliminary Study

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ABSTRACT

Background: Thalidomide is known to have hypnosedative, immuno-modulatory and anti-angiogenic effects. The drug is widely used in several neoplastic disorders, inflammatory conditions and skin disorders. Thalidomide has been successfully used in limited number of adult thalassemia patients. Studies on younger thalassemia patients are lacking.

Objective: Current study aims at exploring efficacy and safety profile of thalidomide in younger thalassemia patients.

Methods: A cohort of 20 randomly selected transfusion dependent thalassemia patients were enrolled into the study. Base-line clinico-haematological and biochemical parameters were recorded for each patient. All the patients were given thalidomide for a period of six months and the response was recorded on monthly basis. Data collected was analysed for statistical significance. Study patients included 16 male and 4 female patients.

Results: Mean age of study patients was 12.8 ± 3.6 years. Mean haemoglobin (Hb) levels, pre and post thalidomide, were 4.8 (±1.5) g/dL and 8.2 (±1.8) g/dL respectively (p-value <0.05). Among study patients, 8 (40%) showed Excellent Response, 7 (35%) showed Good Response, 3 (15%) had Poor Response while 2 (10%) patients did not respond to the treatment. No major side effects of therapy were observed among study patients.

Conclusion: The study concludes that thalidomide significantly raises Hb levels in transfusion dependent thalassemia patients when given in low doses. Safety profile for usage of thalidomide in this group of patients is satisfactory.

Trial Registration:NCT03651102, https://clinicaltrials.gov/ct2/show/NCT03651102

Key Words: Thalassemia, Transfusion Independence, Thalidomide, Safety and Efficacy

Introduction

Haemoglobinopathies are among the most prevalent inherited genetic disorders around the world. Approximately 80 million people, globally, are carriers for β-thalassemia.[1] South Asia is recognized as a hotspot for haemoglobinopathies, especially β-thalassemia.[2] Likewise, the disease is also common in Pakistan. A formal national registry does not exist. It is, however, estimated that around 5000-9000 children are born with the disease annually, with an extrapolated carrier rate of 5-7%.[3]

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Thalassemia management entails an array of therapeutic interventions with packed red blood cells transfusions at one extreme and bone marrow transplantation at the other. The former is compounded by a myriad of complications whereas the latter is delimited by its cost. Recently, United States Food and Drug Administration (FDA)approved a new drug "Luspatercept", for treatment of transfusion dependent thalassemia (TDT) in adults.[4] This primarily is an erythroid maturation agent, trapping inhibitors of late-stage erythropoiesis.[5]

Thalidomide, a synthetic glutamic acid derivative, is known to have hypnosedative, immuno-modulatory and anti-angiogenic effects.[6] Initially the drug was misused as an anti-emetic agent in pregnant women which led to catastrophic teratogenic effects and a consequent withdrawal from the market.[7] The drug however made a strong come back and is widely used in several neoplastic disorders (e.g. multiple myeloma and malignant melanoma), inflammatory conditions

(e.g. Crohn's disease) and skin disorders (e.g. leprosy).[6]

On molecular scale, thalidomide is found to affect the production of vascular endothelial growth factor (VEGF), prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α) and cytokine-induced nuclear factor-κB (NF-κB).[8] The drug increases production of reactive oxygen species (ROS) which has significant impact on expression of several genes and on certain cell signaling pathways.[8]

Thalidomide has been found to augment the production of fetal haemoglobin (HbF). Enhancement of GATA-1, EKLF and γ-globin gene has been established.[9] Several studies have proved the efficacies of thalidomide in adult thalassemia patients.[10-14] Larger studies, however, are underway which will delineate the guidelines. Effects of the drug in pediatric thalassemia patients are not yet explored. The current trial is a pilot study for appraisal of efficacy, tolerance and safety in younger thalassemia patients.

Methods

This off label, single-arm clinical trial was carried out at Blood Diseases Clinic (BDC) Peshawar from January 2018 to July 2018. A total of 20 randomly selected (employing table of random numbers) diagnosed cases of TDT patients of either gender and >9-18 years of age were enrolled into the study after obtaining informed consent from parents/guardians. Those with active systemic comorbidity, with past personal or family history of thrombophilia, recent fracture or recent major surgery were excluded from the study.

A comprehensive questionnaire encompassing demographic and clinical details of the patient was filled out for each participant by a pre-trained physician. General physical and systemic examination was carried out. Transfusion history was recorded in detail. A volume of 2mL and 3mL venous blood samples were collected in plain red-top and purple-top EDTA containing sample collection glass tubes. The EDTA-admixed blood was analysed for complete blood count on automatic haematology analyzer, KX-21® (Sysmex, Kobe, Japan). Serum, drawn from plain tube, was tested for bilirubin, alanine transferase (ALT), creatinine, uric acid and lactate dehydrogenase (LDH) levels on Cobas C111® chemistry analyzer (Roche Diagnostic Systems, Mannheim, Germany) as per manufacturer's guidelines.

Study patients were given thalidomide at an average dose of 1.5mg/kg/day (range 1-3mg/kg/day). Patients were followed at four weeks interval for monitoring of potential side effects and for evaluation of clinical and laboratory response. All the base line investigations were repeated in every visit.

Primary endpoint of this study was haemoglobin (Hb) level measured before the commencement and at the cessation of thalidomide therapy. Consequently, patients served as their own historical controls. Thalidomide therapy was prematurely tapered off before the destined six months period in cases wherein Hb level raised to >9g/dL at a minimum of two months post-transfusion interval. In other cases, it was tapered off after completing full course of study, i.e. six months' time period. Tapering was completed over a course of four-week time.

Response criteria were set as following[15]:

1. Excellent Responders (ExR): In whom Hb level raised to ≥9.0g/dl without any transfusion in the last two months.
2. Good Responders (GR): In whom Hb level raised to 7.0-8.9 g/dL without any transfusion in the last two months.
3. Partial Responders (PR): In whom Hb level remained <7.0 g/dL but did raise by 1g/dL in comparison to the base-line without any transfusion in the last two months.
4. Non-Responders (NR): In whom Hb level did not improve by ≥1 g/dL in comparison to the base-line.

Data obtained was recorded and statistical analyses were carried out in Statistical Package for Social Sciences® (SPSS) version 23 (SPSS Inc. Chicago, IL, USA). For comparison of quantitative study parameters prior to and at cessation of thalidomide therapy, paired samples t-test and Wilcoxon signed ranks test were employed. Quantitative variables were compared among the four response groups using 1-way analysis of variance (ANOVA). Chi-square test was carried out for assessment of nominal data among the groups. P-value of <0.05 was regarded as statistically significant.

Results

A total of 20 TDT patients (16 male and 4 female), with a mean age of 12.8 ± 3.6 years, were enrolled into the study. Patients were given low dose thalidomide for a period of 30 weeks. Three patients (15%) were previously splenectomized. All the patients completed the six months follow up. In seven cases thalidomide was tapered off before the stipulated 6 months' time period. Achieving ExR status before the stipulated six

months' time was the only reason for early drug withdrawal.

Response in Hb level was the primary end point in this trial. Among study patients, 8 (40%) showed ExR, 7 (35%) showed GR, 3 (15%) had PR while 2 (10%) patients did not respond to the treatment. The Hb level did not deteriorate with thalidomide therapy in any patient. The overall response to treatment remained comparable among the two genders and no significant variation was observed (p-value 0.65). Among the four female patients, two had ExR, a single patient showed GR and the last patient did not show any response (**FIGURE 1**).

The pre and post thalidomide Hb levels were compared among the study patients employing Paired Samples T-test. The pre and post thalidomide therapy difference in white blood cell (WBC) and platelet counts was insignificant (**TABLE 1**).

All the patients enrolled into the study were transfusion dependent. However, after commencing thalidomide therapy, only four patients required further transfusions. All of these were from the PR and NR groups. The two patients from NR group were regularly transfused at 2-5 weeks interval whereas PR group patients (n=2) required transfusion at 4-6 weeks intervals.

Side effects observed included skin rash (n=1, 5%) and gastrointestinal symptoms, i.e. nausea (n=2, 10%) and constipation (n=3, 15%). Dose reduction in those with skin rash and symptomatic use of oral laxative (lactulose) in patients with constipation relieved the symptoms. The drug was not withdrawn in any case due to side effects. Biochemical profile remained within normal range in all the study patients for the entire period of study.

TABLE 1: Study variables before and after thalidomide therapy

Test Parameters	Phase	Mean	Std. Deviation	p-value*
Weight (kg)	Pre-therapy	30.12	12.81	.071
	Post-therapy	30.73	13.46	
Hb (g/dL)	Pre-therapy	4.89	1.49	.000
	Post-therapy	8.29	1.78	
WBCs ($x10^9$/L)	Pre-therapy	11.16	21.51	.563
	Post-therapy	8.96	7.25	
Platelets ($x10^9$/L)	Pre-therapy	294.05	195.42	.057
	Post-therapy	354.30	189.84	
RBCc ($x10^{12}$/L)	Pre-therapy	2.28	1.03	.003
	Post-therapy	3.55	.67	
Hct (L/L)	Pre-therapy	16.63	6.67	.001
	Post-therapy	26.22	3.98	
MCV (fL)	Pre-therapy	72.17	4.25	.051
	Post-therapy	74.36	5.41	
MCH (pg)	Pre-therapy	23.71	2.25	.193
	Post-therapy	24.06	1.98	
MCHC (g/dL)	Pre-therapy	32.85	1.77	.330
	Post-therapy	32.36	1.24	
RDW (%)	Pre-therapy	59.08	11.28	.009
	Post-therapy	67.34	11.76	
Bilirubin (g/dL)	Pre-therapy	.86	.57	.494
	Post-therapy	.99	.55	
ALT (U/L)	Pre-therapy	31.83	11.75	.486
	Post-therapy	28.17	10.55	
Creatinine (mg/dL)	Pre-therapy	.37	.17	.127
	Post-therapy	.46	.22	
Uric Acid (mg/dL)	Pre-therapy	2.88	.39	.053
	Post-therapy	3.65	1.22	
LDH (mg/dL)	Pre-therapy	250.92	45.92	.34
	Post-therapy	275.67	69.67	

***Paired Samples T-test employed**

ALT, Alanine Transaminase; Hb, Haemoglobin; LDH, Lactate Dehydrogenase; MCH, Mean Corpuscular Haemoglobin; MCHC, Mean Corpuscular Haemoglobin Concentration; MCV, Mean Corpuscular Volume; RBCc; Red Blood Cells Count; RDW, Red Cell Distribution Width; WBCs, White Blood Cells Count

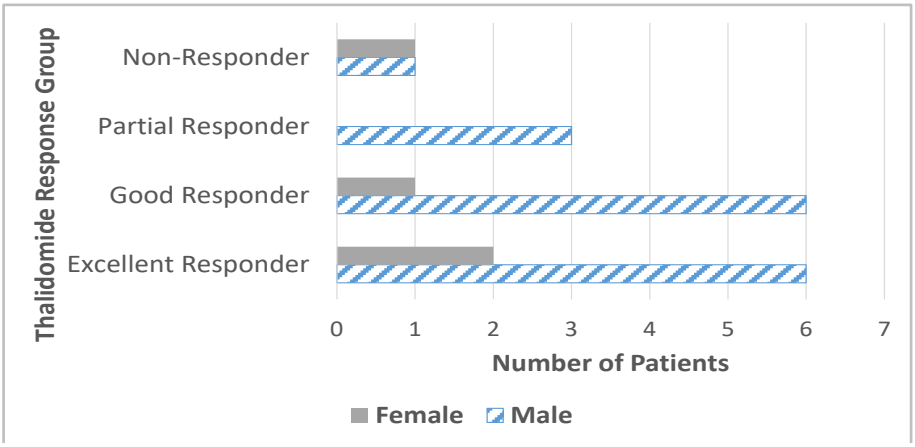

FIGURE 1. Thalidomide response among male and female patients

Discussion

Owing to cumulative lethal complications over time, majority of the TDT patients, in the affected parts of the world, are from younger age groups.[16] Effects of thalidomide have been observed in only a limited number of adult thalassemia patients.[10-14, 17] To our knowledge, current is the first study exploring efficacy and safety of the drug among children suffering from TDT.

Pre and post thalidomide therapy mean Hb levels, in patients from current study, were 4.8mg/dL and 8.2mg/dL, respectively. This increase in Hb level is comparable to the one found among 15 Chinese patients in two separately conducted studies.[11,14] A similar response has also been reported in limited number of Italian, Albanian and Mexican patients as well.[10,12,13,17] Molecular basis of increase in Hb levels with thalidomide implicates induction of γ-globin expression in adult erythroid progenitor cells. This process is, in turn, mediated by ROS-dependent activation of p38 mitogen-activated protein kinase (MAPK) pathway and acetylation of histone H4.[8] Besides, an increase in erythropoiesis is also documented.[17] In-vivo analysis of these phenomena in thalassemia patients has not yet been undertaken. As to what did actually lead to the increase in Hb levels could not be tackled in the current study. A study focusing this aspect is suggested to be carried out in larger groups of patients to definitively elucidate the query.

In current study, thalidomide was given in low doses, i,e, 1-3mg/kg. As anticipated, only mild side effects, including, skin rash, nausea and constipation, were observed. The biochemical profile also remained satisfactory for the entire period of study. Previously conducted studies also reported similar safety profile. In the first ever study describing role of thalidomide in thalassemia, the 21-year-old splenectomized patient received thalidomide for six years at a dosage of 100mg/day without any significant side effect.[17] Other studies conducted later, on patients from different ethnic groups, showed similar safety profile for thalidomide in thalassemia.[10-14] The remarkably safe profile described in these studies portray extensive historical experience with the drug. Keeping in mind the potential harmful effects associated with the drug, an enhanced level of careful handling and monitoring among the patients is ensured among the patients in current as well as previous studies.

With advancements in health care, management of TDT has greatly improved in the last few decades.[18] In Pakistan; however, the average life expectancy for TDT patients is still around 10 years.[19, 20] This mainly relates to the inadequacy of management in local settings. The inadequacy, in turn, pertains to the exorbitant expense of appropriate iron chelation, transfusions, disease monitoring and management of related complications. Thalidomide is an inexpensive drug, costing around 10 dollars per month in an average TDT child. The drug may therefore prove ground breaking in thalassemia management, especially in developing countries. A rather meticulous study, on larger cohorts of patients, is warranted for definitive recommendation.

Conclusion

The study concludes that thalidomide significantly raises Hb levels in TDT patients when given in low doses. The safety profile for usage in this group of patients is satisfactory.

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Conflict of Interest: Authors declare no conflict of interest.

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