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ORIGINAL ARTICLE

SAFETY AND EFFICACY OF THALIDOMIDE IN TRANSFUSION-DEPENDENT β-THALASSEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

OBJECTIVE: The current meta-analysis was carried out to identify the efficacy and safety of thalidomide in transfusion-dependent β-thalassemia (TDT) patients.

METHODS: Six databases: PubMed, EMBASE, Scopus, Cochrane Library, EBSCOhost, and MEDLINE were searched until November 18, 2021, for studies that assessed the efficacy of thalidomide in TDT patients by using the following search terms: "Thalidomide", "thalidomid", "thalomid", "N-phthaloylglutamimide", and Thalassemia" using Boolean or wildcard operators. Original research publications in English with observational and/or experimental designs having a sample size ≥10, regardless of age and gender, used thalidomide for ≥3 months exploring the impact of thalidomide in ameliorating transfusion needs among TDT patients were included in this meta-analysis. Data were independently extracted by two reviewers using a data extraction form. The National Institutes of Health tool was used for quality assessment.

RESULTS: Nine studies collectively involving 407 TDT patients fulfilled eligibility criteria. Thalidomide was associated with complete cessation of blood transfusion requirements with an overall response of 54% (95% CI, 34–75%) to a transfusion-independent state; heterogeneity was considered high with an I^2 of 94.7%, p-value<0.001. Mild adverse events were reported in 44% of patients.

CONCLUSION: Thalidomide is a well-tolerated, effective and safe drug among TDT patients, these findings, however, should be confirmed through well-designed clinical trials.

PROSPERO Review registration number: CRD42021289950.

Keywords: Safety (MeSH); Efficacy (Non-MeSH); Thalidomide (MeSH); Transfusion-dependent β-thalassemia (Non-MeSH); Thalassemia (MeSH); beta-Thalassemia (MeSH); Anemia, Hemolytic, Congenital (MeSH)

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INTRODUCTION

β-thalassemia is characterized by low hemoglobin levels and is considered the most common inherited disease around the globe.[1] Thalassemia is mostly found in Central Asia, the Mediterranean, the Middle East, Southern China and India, however due to migration, it is now a global phenomenon.[1] The global incidence of abnormal hemoglobin and thalassemia is approximately 270 million, of which 80 million individuals are β-thalassemia carriers.[2]

β-thalassemia, based on blood transfusion requirement is classified into transfusion dependent β-thalassemia (TDT) and non-transfusion-dependent β-thalassemia (NTDT).[3] In TDT patients, regular blood transfusion is regarded as the mainstay of treatment.[1,4,5] However, chronic blood transfusion pose a significant risk of iron overload and subsequent multi-organ damage, as well as acute life-threatening events such as acute hemolytic reactions, bacterial infections and anaphylaxis.[6]

Owing to the risks and limitations of chronic blood transfusions, the efficacy of different drugs has been investigated in order to improve the patients' quality of life.[7] Thalidomide (an immuno-modulating drug) showed promising results in increasing hemoglobin levels and reducing blood transfusion needs in patients with β-thalassemia.[8,9] Despite the fact that several studies [8-11] have reported promising response of thalidomide in TDT, it is still overlooked in the practice guidelines as a treatment option for β-thalassemia management.

Current literature is partial due to lack of precise meta-analyses reporting the efficacy of thalidomide in reducing/ceasing transfusion needs among TDT patients. We believe that a meta-analysis exploring the efficacy of thalidomide in the complete cessation of transfusion needs among TDT patients will certainly change the current practice of how TDT patients are treated by filling the partially explained gap in knowledge. Therefore, this study aimed to determine the efficacy of thalidomide as a potential treatment in ameliorating transfusion needs among TDT patients by performing a rigorous meta-analysis.

METHODS

Data Sources and Search Strategy

A comprehensive systematic search of the literature using six databases (PubMed, EMBASE, Scopus, Cochrane Library, EBSCOhost, and MEDLINE) was conducted to evaluate the clinical efficacy and safety of thalidomide in TDT patients requiring regular blood transfusions regardless of age and gender until November 18, 2021. All databases were searched using the following search terms: "Thalidomide", "thalidomid", "thalomid", "N-phthaloylglutamimide", and Thalassemia" using Boolean or

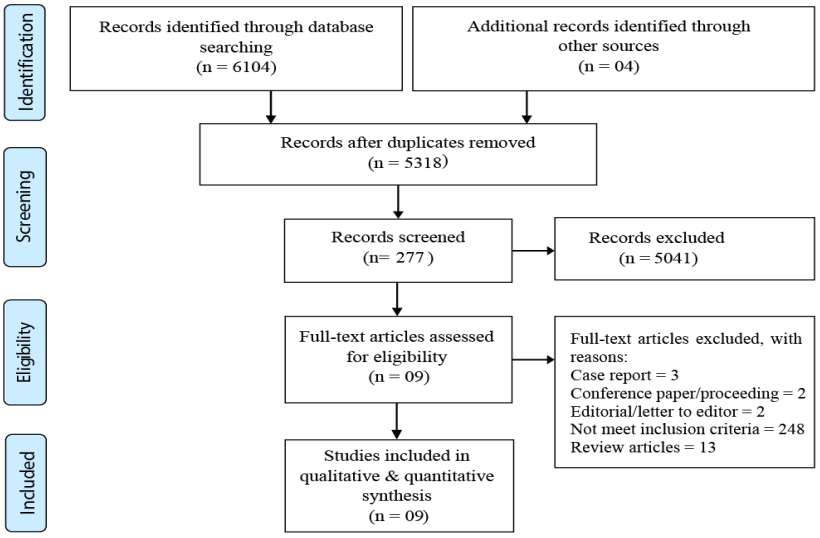

Figure 1: PRISMA flow chart of the included studies

wildcard operators. Complete description of the search terms is presented in **Appendix 1**. Reference lists of all primary studies were also screened and searched using hand searches in order not to miss any potential study. Moreover, to find potential studies, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed.[12]

Study Selection

Original research publications in English with observational and/or experimental designs having a sample size ≥10, regardless of age and gender, used thalidomide for ≥3 months exploring the impact of thalidomide in ameliorating transfusion needs among TDT patients were included in the meta-analysis. Patients with NTDT, β-thalassemia intermedia (TI), systematic reviews, case series, case reports, and conference abstracts were not eligible for inclusion. If an article included both NTDT and TDT patients, patients with TDT treated with thalidomide were included, while others were excluded.

Data Extraction and Quality Assessment

Data were independently extracted by two reviewers (Z.A and M.I) using a data extraction form. Any disagreement was resolved between reviewers by discussion until consensus was reached. The following data were extracted: author, year, country of publication, study design, sample size, age, follow up duration, thalidomide dose, blood transfusion independence rate, and adverse events from all included studies. The quality of the included studies was assessed using the National Institutes of Health (NIH) quality assessment tool for pre-post studies with no control group.[13]

Data Analysis

STATA (v-14) was utilized for performing meta-analyses using the random-effects model vs the fixed-effects model because of expected heterogeneity within and between studies.[14] Among the included studies, I^2 statistic was used to interpret the heterogeneity at a confidence interval of 95%.

RESULTS

Study Selection

The initial literature search yielded 5318 references after duplicates were removed. One author (Z.A.) then screened the titles and abstracts of 5318 references, of which 277 references were selected. Upon the application of inclusion and exclusion criteria of the remaining 277 references, 9 articles were included for meta-analyses and 268 references were excluded because of the following reasons: 248 studies were not meeting inclusion criteria, 13 were review articles, 2 each were conference proceedings and letter to editors, and 3 were case reports (Figure 1).

Study Characteristics

Characteristics of all included studies are presented in Table 1. All included studies were conducted between 2017 and 2021 in five countries: three in China, three in India, and one each in Bangladesh, Iraq and Pakistan. All studies were single-arm with no comparison group and of pre-post design, of which six studies were conducted prospectively while three were retrospective studies.[8,15] All studies collectively enrolled 407 patients and were published in English as full-text articles. The sample size ranged from n=12 to 102 and was a mixture of children and adults (age range= 1-45 years).

TABLE I: CHARACTERISTICS OF THE INCLUDED STUDIES

Author	Country	Design	Disease	Population	Sample Size (N=407)	Age* (Range) in years	Thal Dose (mg/kg/d	Tx Indep	Follow-up (months)
Li, 2021 [8]	China	Pre-post	β-TM	TDT	77	10 (5-18)	2.5-4	51	6
Chandra, 2021 [10]	India	Pre-post	HbE-β-TM	TDT	37	14.7 (12-18)	2-4	15	6
Begum, 2020 [9]	Bangladesh	Pre-post	HbE-β-TM	TDT	51	10 (3-24)	2-5	18	32
Yang, 2020 [19]	China	Pre-post	β-TM	TDT	12	27.7 (NR)	50a	5	3
Nag, 2020 [15]	India	Pre-post	HbE-β-TM	TDT	21	20**(NR)	50-100a	15	3
Yang, 2020 [18]	China	Pre-post	β-TM	TDT	23	27.2 (15-45)	50-100a	10	24
Yassin, 2019 [11]	Iraq	Pre-post	β-TM	TDT	14	10** (3-43)	2-10	5	8-36
Jiskani, 2018 [16]	Pakistan	Pre-post	β-TM	TDT	70	10.3 (7-12)	2-10	0	6
Vijay, 2017 [17]	India	Pre-post	β-TM	TDT	102	13 (1-36)	2-10	95	6-24

(a): mg/day, (*): Mean age; (**): Median age, N: Total Sample Size, NR: Not Reported, TDT: Transfusion Dependent β-thalassemia, Thal: Thalidomide, Tx Indep: Transfusion Independence

TABLE II: NATIONAL INSTITUTES OF HEALTH QUALITY ASSESSMENT TOOL

Criteria	Li, 2021	Chandra, 2021	Begum, 2020	Yang, 2020	Nag, 2020	Yang, 2020	Yassin, 2019	Jiskani, 2018	Vijay, 2017
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	No	Yes	Yes	No	No	No
3. Were the participants in the study representative of those who would be eligible for the test/service/ intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	CD	Yes	CD	Yes	CD	CD	CD
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	Yes	Yes	No	No	No	No	Yes	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	No	No	No	No	No	No	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quality Rating	Good	Good	Good	Fair	Good	Good	Fair	Fair	Fair

CD: Cannot Determine; NA: Not Applicable

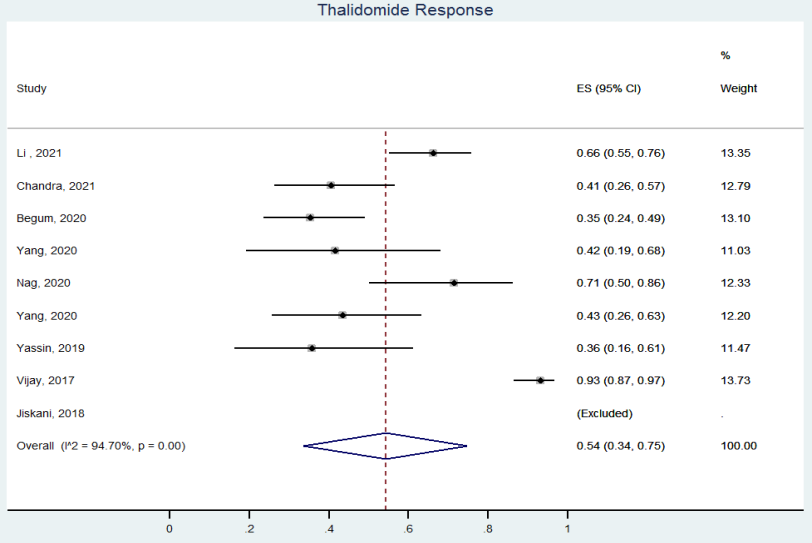

Figure 2: Forest plot of thalidomide response rate (transfusion-independence) in transfusion-dependent β-thalassemia patients

All patients were transfusion dependent and thalidomide was the only intervention except regular blood transfusions. Thalidomide was given orally as a single dose in the range of 2-10mg/kg/day in six studies,[8-11,16,17] and 50-100mg/day in three studies.[15,18,19] Of the included studies, pre/post serum ferritin levels are reported by seven studies,[9-11,15-18] Hb levels by six studies[9,10,15,16,18,19] and HbF percentage by four studies.[8,10,18,19] The average baseline serum ferritin level was significantly decreased except one study[18] in which after treatment a significant increase in average serum ferritin level was noted. Hb levels as compared to baseline significantly increased after treatment. A study by Chandra et al.[10] reported a slight decrease in Hb level after treatment; however, the rate of fall of Hb significantly decreased after treatment

TABLE III: LIST OF ADVERSE EVENTS REPORTED IN THE INCLUDED STUDIES

Author (Year)	Adverse Events									
Li, 2021[8]	Dizziness/ lethargy	Consti-pation	Neutro-penia	Leukocy-topenia	Thromb-ocytosis	CVT*	Seizure*	Vomiting/ nausea	Arthralgia	Edema
Chandra, 2021[10]	Constipation	Neutro -penia	Pneumo-nia	Chicken pox	Acute febrile illness	Dengue infection	Dizziness*	AKI*	Sedation	-
Begum, 2020[9]	High ALT	Palpitat-ions	Excessive sleepiness	Restless-ness	Acute urticaria	Facial puffiness	Cough	Vomiting	High TSH	Edema
Yang, 2020[19]	-	-	-	-	-	-	-	-	-	-
Nag, 2020[15]	Constipation	-	-	-	-	-	-	-	-	-
Yang, 2020[18]	Peripheral neurotoxicity*	Rash	Menstrual disorder	GIT disorders	-	-		-	-	-
Yassin, 2019[11]	Constipation	EHAM*	-	-	-	-	-	-	-	-
Jiskani, 2018[16]	-	-	-	-	-	-	-	-	-	
Vijay, 2017[17]	DVT*	Gynecomastia	-	-	-	-	-	-	-	-

EHAM: Extramedullary Hemopoietic Abdominal Masses, AKI: Acute Kidney Injury, ALT: Alanine Aminotransferase, CVT: Central Venous Thrombosis, DVT: Deep Vein Thrombosis, GIT: Gastrointestinal Tract, TSH: Thyroid-stimulating hormone, (*): Patients withdrew thalidomide due to adverse event (s)

with thalidomide. A total of four studies measured HbF percentage and showed a significant increase in HbF percentage after thalidomide treatment. One study[18] measured LDH and bilirubin levels and reported a significant decrease in both LDH and bilirubin levels after treatment. None of the other studies measured LDH and bilirubin levels.

Of the included studies, the follow-up duration of TDT patients was in the range of 3-32 months in order to determine the safety and efficacy of thalidomide. The mean follow-up duration was approximately 12 months. Two studies[15,18] measured spleen size before and after treatment, but no statistically significant difference was found.

Quality Assessment of included studies

The NIH quality assessment tool for pre-post studies without a control group was employed for the quality appraisal of the included studies (Table II). Five eligible studies were rated as of good quality, and four of fair quality. The following methodological limitations were noted; small sample size in four studies, and lack of prespecified eligibility criteria in the majority of the studies. Moreover, none of the studies stated whether assessing the outcomes were blinded or not which may bias the findings.

Thalidomide Response

Thalidomide was associated with complete cessation of regular blood transfusion among TDT patients with an overall response of 54% (95% CI, 34–75%) to a transfusion-independent state; heterogeneity was considered high with an[12] of 94.7%, p-value<0.001; as depicted in Figure II. One study[16] was excluded in the forest plot generation because of no response (0% response rate).

Adverse Events

Adverse events (AEs) related to thalidomide are presented in Table III. All studies reported AEs except two studies.[16, 19] Mild AEs were reported in 44% of the patients except one episode of grade-III neutropenia and one episode of grade-IV acute kidney injury. Thalidomide was well tolerated among most of the patients, only 8 (2%) patients stopped using thalidomide due to AEs (deep vein thrombosis (n=2)[17], cerebral venous thrombosis (n=1),[8] seizure (n=1),[8] extramedullary hemopoietic multiple abdominal masses (n=1) which disappeared upon starting hydroxyurea,[11] dizziness (n=1), and acute kidney injury (n=1).[10] One patient developed peripheral neurotoxicity and intermittent numbness in lower limbs at 18 months of treatment; however, symptoms were not completely reversed after stopping thalidomide for four subsequent months.[18] Constipation (n=43, 10.6%)[8,10,11,15], dizziness and/or lethargy (n=29, 7.1%),[8,10] neutropenia (n=20, 4.9%),[8,10] nausea/vomiting (n=10, 2.4%),[8,9] and thrombocytosis (n=9, 2.2%)[8] were more frequently reported AEs followed by High ALT (n=8, 2%)[9], leukocytopenia (n=7, 2.3%), sedation[9,10] and elevated d.dimers[10] (n=6 each, 1.5%), edema[8,9] (n=4, 1%) and deep vein thrombosis and gynecomastia (n=2 each, 0.5%)[17], and thyroid-stimulatingulating hormone (n=2, 0.5%)[9]. None of the patients with elevated d.dimers presented with thromboembolism.[10]

DISCUSSION

This meta-analysis was aimed to determine the safety and efficacy of thalidomide among TDT patients. Eight single-arm studies, of pre-post design with no comparison group met our inclusion criteria, of which six were prospective studies and three were retrospective. These studies collectively enrolled 407 patients requiring regular blood transfusion. Results of the current meta-analysis revealed that 54% of TDT patients become transfusion independent after treatment with thalidomide. Heterogeneity among the included studies was high, which may be attributed to different sample sizes of the included studies.

As far as AEs are concerned, in majority of the eligible studies it was narratively reported, therefore we could not perform meta-analysis on AEs related to thalidomide use. Majority of the AEs were transient, and relieved spontaneously without withdrawal of the drug, only eight patients stopped taking thalidomide due to AEs.[8, 10, 11, 17] On few occasions the AEs relieved after lowering the dose or temporary cessation of the drug. Constipation and neutropenia were the most commonly reported AEs in the included studies.

The mean follow-up duration of all patients in the included studies was approximately 12 months, therefore the incidence of long term AEs was not documented. Acute kidney injury occurred in one patient,[10] although the patient was taking deferasirox (a well-known nephrotoxic drug).[20,21] Further, no case of mortality directly related to thalidomide was reported, only one patient died due to dengue shock which the patient developed during the second month of treatment with thalidomide.[10]

None of the included study assessed the patient's quality of life (QoL), although it is

obvious that the complete cessation of blood transfusion and /or reducing transfusion needs would have certainly improved the QoL. However, long-term studies assessing impact of thalidomide treatment on QoL are highly advocated.

TDT patients require regular blood transfusions for survival, however chronic blood transfusions pose a significant burden on healthcare system in developing countries where the prevalence of thalassemia patients is usually high. Chronic blood transfusions may cause iron overload and subsequent multi-organ damage, as well as acute life-threatening events. Therefore, owing to the limitations of regular blood transfusion, thalidomide is an economical drug and costs each patient around 5-10$ per month. Conversely, in the same patients' blood transfusion followed by adequate chelation costs 60-80$.[22] One study reported that for an average 70kg adult, one unit of blood cost 316$, while chelation with deferoxamine and deferasirox for a one-month supply costs 1,500$ and 3,760$, respectively.[23]

This meta-analysis suggests the potential role of thalidomide therapy in the complete cessation of transfusion needs, despite the above-mentioned limitations and lack of robust experimental studies. Based on the findings of this meta-analysis as well as complications associated with chronic blood transfusions, the quick response of TDT patients' to thalidomide (in months), easy availability as well as affordability of thalidomide particularly in developing countries, we recommend the usage of thalidomide in treating children and adults with TDT. Therefore, until stringent clinical studies such as well-designed randomized control trials are conducted, the authors concluded that thalidomide may be prescribed to TDT patients for a minimum of 3 to 6 months along with a well-designed monitoring plan to ensure the safety and efficacy, after obtaining informed consent from the patient itself (if he/she is an adult) or the parents/guardian (if the patient is a minor).

Limitations of this meta-analysis includes; small sample size, short follow-up duration for thalidomide treatment (mean follow-up~12 months), less number of observational studies and absence of control group in the included studies, respectively. On the other hand, the following are the major strengths of this meta-analysis: (a) this meta-analysis is unique in its kind evaluating the role of thalidomide in the complete cessation of blood transfusions among TDT patients, (b) only TDT patients requiring regular and lifelong blood transfusions are included, NTDT and TI or mixture of both were excluded, (c) furthermore, literature was extensively searched using six major biomedical databases along with journals of potential interest via additional hand search.

REFERENCES

1. Algiraigri AH, Wright NA, Paolucci EO, Kassam A. Hydroxyurea for lifelong transfusion-dependent β-thalassemia: a meta-analysis. Pediatr Hematol Oncol 2017;34(8):435-48. https://doi.org/10.1080/08880018.2017.1354948
2. De Sanctis V, Kattamis C, Canatan C, Soliman AT, Elsedfy H, Karimi M, et al. β-thalassemia distribution in the old world: an ancient disease seen from a historical standpoint. Mediterr J Hematol Infect Dis 2017;9(1):e2017018. https://doi.org/10.4084/mjhid.2017.018
3. Barnett, R. Thalassaemia. The Lancet. 2019;394(10204):1135 https://doi.org/10.1016/s0140-6736(19)32169-5
4. Cappellini M, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Blood Transfusion Therapy in β-Thalassaemia Major. Chapter 2. In: Guidelines for the Clinical Management of Thalassaemia. 2nd Revised edition. Thalassaemia International Federation; 2008. Accessed on: December 06, 2021. Available from URL: https://www.ncbi.nlm.nih.gov/books/NBK173967/
5. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. Blood 2011;118(13):3479-88. https://doi.org/10.1182/blood-2010-08-300335
6. Vichinsky E, Neumayr L, Trimble S, Giardina PJ, Cohen AR, Coates T, et al. Transfusion complications in thalassemia patients: a report from the Centers for Disease Control and Prevention (CME). Transfusion 2014;54(4):972-81. https://doi.org/10.1111/trf.12348
7. Longo F, Piolatto A, Ferrero GB, Piga A. Ineffective Erythropoiesis in β-Thalassaemia: Key Steps and Therapeutic Options by Drugs. Int J Mol Sci 2021;22(13):7229. https://doi.org/10.3390/ijms22137229
8. Li X, Hu S, Liu Y, Huang J, Hong W, Xu L et al. Efficacy of thalidomide treatment in children with transfusion dependent β-thalassemia: a retrospective clinical study. Front Pharmacol 2021;12:722502. https://doi.org/10.3389/fphar.2021.722502
9. Begum M, Moslem MHM, Begum NNF, Rahman MZ. Outcome of treatment with thalidomide in transfusion dependent thalassemia patients: a prospective study in a Thalassemia Center, Dhaka, Bangladesh. Am J Pediatr 2020;6(3):168-71. http://dx.doi.org/10.11648/j.ajp.20200603.11
10. 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):611-6
11. Yassin AK. Promising response to thalidomide in symptomatic β-thalassemia. Indian J Hematol Blood Transfus 2020;36(2):337-41. https://doi.org/10.1007/s12288-019-01231-5
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
13. National Institte of Health (NIH). Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group. Accessed on: December 10, 2021. Available from URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
14. StataCorp L. StataCorp stata statistical software: Release 15. StataCorp LP: College Station, TX, USA 2017.
15. Nag A, Radhakrishnan VS, Kumar J, Bhave S, Mishra DK, Nair R, et al. Thalidomide in patients with transfusion-dependent E-beta thalassemia refractory to hydroxyurea: a single-center experience. Indian J Hematol Blood

Transfus 2020;36(2):399-402. https://doi.org/10.1007/s12288-020-01263-2

16. Jiskani SA, Memon S. Effect of thalidomide in patients with β–thalassemia major. Hematol Transfus Int J 2018;6(6):234-6. https://doi.org/10.15406/htij.2018.06.00191
17. Ramanan V, Kelkar K. Role of thalidomide in treatment of beta thalassemia. J Blood Disord Med 2017;3(1):8-10. http://dx.doi.org/10.16966/2471-5026.119
18. Yang K, Wu Y, Zhou Y, Long B, Lu Q, Zhou T, et al. Thalidomide for patients with β-thalassemia: a multicenter experience. Mediterr J Hematol Infect Dis 2020;12(1):e2020021. https://doi.org/10.4084/mjhid.2020.021
19. Yang K, Wu Y, Ma Y, Xiao J, Zhou Y, Yin X. The association of HBG2, BCL11A, and HBS1L-MYB polymorphisms to thalidomide response in Chinese β-thalassemia patients. Blood Cells Mol Dis 2020;84:102442. https://doi.org/10.1016/j.bcmd.2020.102442
20. Díaz-García JD, Gallegos-Villalobos A, Gonzalez-Espinoza L, Sanchez-Niño MD, Villarrubia J, Ortiz A. Deferasirox nephrotoxicity—the knowns and unknowns. Nat Rev Nephrol 2014;10(10):574-86. https://doi.org/10.1038/nrneph.2014.121
21. Oda K, Katayama K, Tanoue A, Murata T, Hirota Y, Mizoguchi S et al. Acute kidney injury due to thin basement membrane disease mimicking Deferasirox nephrotoxicity: a case report. BMC Nephrol 2018;19(1):1-6. https://doi.org/10.1186/s12882-018-1180-2
22. Khan MTM. Thalidomide in Thalassemia: A Fortune in Making. Int J Pathol 2019;17(3):97-98
23. Delea TE, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, Coates TD. Cost effectiveness of once-daily oral chelation therapy with Deferasirox versus infusional Deferoxamine in Transfusion-dependent Thalassaemia patients. Pharmacoeconomics 2007;25(4):329-42. https://doi.org/10.2165/00019053-200725040-00005

APPENDIX I

Description of Search terms

"thalassaemia OR thalassemia OR Betathalassemia OR Beta-thalassaemia OR β-thalassaemia OR β-thalassemia OR b-thalassemia OR b-thalassaemia OR Alpha-thalassemia OR α-thalassemia OR Alpha-thalassaemia OR α-thalassaemia OR Sickle Cell Disease OR Sickle Cell Dis* OR SCD OR Anemia OR Anaemia OR Transfusion-dependent thalassemia OR Transfusion-dependent thalassaemia OR Blood transfu* OR hemoglobin synthesis OR haemoglobin OR hemoglobin OR fetal hemoglobin OR foetal hemoglobin OR foetal haemoglobin OR fetal haemoglobin OR HBF OR Fetal Hemoglobin Induc* OR Foetal Hemoglobin Induc* OR Foetal Haemoglobin Induc* OR Fetal Haemoglobin Induc* OR Hb F induc* AND Thalidomide OR thalidomid OR thalomid OR N-phthaloylglutamimide."

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

ZA: Conception & study design, Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

MI: Acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

MTMK & IUR: Analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors declared no specific grant for this research from any funding agency in the public, commercial or non-profit sectors

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request