Clinical Research

Efficacy of fetal hemoglobin inducers in adult transfusion-dependent beta-thalassemia patients: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND Patients with transfusion-dependent beta-thalassemia (TDBT) face risks of iron overload, which also burdens national expenditures in Indonesia. Elevated fetal hemoglobin (HbF) expression is associated with reduced blood transfusion dependency. This study aimed to assess the efficacy and safety profile of HbF inducers as adjuvant therapy for adult patients with TDBT and appraise its feasibility for Indonesian patients.

METHODS This study analyzed 7 trials of HbF inducers, such as hydroxyurea, thalidomide, butyrate, and decitabine, in 382 adult participants (mean age >16), including 28 patients with non-TDBT. Outcomes assessed included hemoglobin (Hb) levels, transfusion needs, and adverse events (AEs). Studies were sourced from PubMed, Cochrane, Embase, and individual searches. The standardized mean difference (SMD) was used as the primary effect size. The protocol was registered in PROSPERO (CRD4202454646368).

RESULTS High heterogeneity was observed, with HbF inducers associated with a significant decrease in transfusion needs (SMD = −0.88; 95% confidence interval [CI] = −1.37 to −0.26); I^2 = 79%, P_{χ_2}<0.01). No significant change in Hb levels was found (SMD = 0.11; 95% CI = −0.69 to 0.91; I^2 = 90%, P_{χ_2}<0.01). The most common AEs were transaminitis and cytopenias, which were tolerable and alleviated upon dose cessation.

CONCLUSIONS HbF induction agents can be used as adjuvant therapy for TDBT, considering their cost-effectiveness, efficacy, and safety profiles.

KEYWORDS beta-thalassemia major, blood transfusion, safety, treatment outcome

Transfusion-dependent beta-thalassemia (TDBT) is an autosomal recessive beta-globin chain hemoglobinopathy characterized by the ineffective synthesis of hemoglobin A (HbA).[1–3] Globally, about 1.5% of the population carries the beta-thalassemia allele, while approximately 3–10% of Indonesia's population is estimated to be carrier. Each year, around 5,000 children in Indonesia are born with beta-thalassemia.[2] According to the Indonesian national guidelines for the management of beta-thalassemia, the main treatment consists of blood transfusion and iron chelation therapy, with special nutritional care and splenectomy as a last resort.[4] However, many of the Indonesian TDBT patients require regular transfusion on a weekly and biweekly basis, which raises concerns over iron overload. While this complication is managed with iron chelation therapy, patients often experience unsatisfactory results for multiple reasons. Additionally, recurrent transfusions can carry the risk of hematogenous infections and rely heavily on the blood

supply. Therefore, alternative or additional treatment modalities are required to suppress transfusion and alleviate the disease burden.

Patients with hereditary persistence of fetal hemoglobin and homozygous beta-thalassemia genotypes showcase a minor to asymptomatic thalassemia phenotype, suggesting that high levels of fetal hemoglobin (HbF) correlate with better clinical manifestation.[2,3] This is due to increased expression of HbF, a hemoglobin species independent of the beta-globin subunit, which replaces the expression of the faulty HbA, which is the pathogenesis of beta thalassemia.[5] This can be induced pharmacologically by using HbF inducers, which have been widely investigated and implemented in several countries, including China, India, Bangladesh, Iraq, Malaysia, and Thailand. Studies have shown that these agents may increase individuals' quality of life by reducing transfusions, alleviating symptoms, and decreasing the risk of iron overload and transfusion-related infection.[3] Furthermore, lowering the need for recurrent transfusion may significantly reduce the overall cost of TDBT management.

Despite the high prevalence of TDBT in Indonesia, HbF inducers have not yet been implemented nationally.[4] The current evidence regarding the efficacy and feasibility of HbF inducers in Indonesia remains inconclusive. Therefore, this study aimed to examine the potential of HbF inducers as an adjunct therapy for patients with TDBT, especially adults, as well as to determine their feasibility and cost-effectiveness in Indonesia.

METHODS

Study protocol and searching strategy

The study followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, and the record screening process followed the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Eligible studies included human intervention studies, randomized controlled trials (RCTs), and cohort, case-control, and case studies investigating the use of HbF inducers, such as hydroxyurea (HU), butyrate, and other cytidine analogs, decitabine, and thalidomide, in adult patients with thalassemia major phenotypes, genotypically confirmed beta-thalassemia, or hemoglobinopathies/beta-thalassemia variants (e.g., HbE/beta-thalassemia). Only studies involving genotypically confirmed patients with beta-thalassemia who had no record of previous treatment with inducers were included. Studies on non-chemotherapy HbF-inducing therapies, such as gene therapy and bone marrow transplantation, were excluded.

A comprehensive literature search was performed across four major medical databases, PubMed (MEDLINE), Cochrane, Embase, and individual searches, using the keywords displayed in Supplementary Table 1. The entire protocol was registered in PROSPERO (CRD4202454646368). Screening and selection of records were conducted in February 2023, and duplicate and ineligible studies were removed.

Data extraction, critical appraisal, and qualitative evidence synthesis

Two authors (MAN and AF) performed data extraction, assessment, and cross-checking for accuracy. Any discrepancies were resolved through discussions with a third author (IR). The extracted data comprised study characteristics (author and year of publication, sample size, and location), patient characteristics (genotype, phenotype, pretreatment baseline Hb levels, age, and follow-up loss rate), intervention details (follow-up duration, regimen, and cotreatment), primary outcomes (Hb level change and transfusion needs, measured in SMD), and secondary outcomes (adverse events and notable miscellaneous findings).

The included records reported outcomes with several effect sizes; therefore, Cohen's *d* was used as the main effect size. Risk of bias (RoB) was assessed using RoB in non-randomized studies of interventions for non-randomized clinical trials, and RoB 2 for RCTs. Finally, the quality of evidence was assessed and presented in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) format.[6]

Meta-analysis, heterogeneity, and subgroup analysis

Data regarding the Hb change and transfusion needs change were analyzed using the Rstudio version 2022.07.2+576 (Posit, USA), through the "meta" and "metasens" packages. The random effect inverse variance method was used to estimate the effect size (standardized mean difference [SMD] for numerical outcome and relative risk for categorical outcome).[7] Heterogeneity was assessed using chi-square and I^2 statistics, with I^2 values >40.00%, suggesting high

heterogeneity. Several study arms were analyzed, and subgroup analyses were conducted based on intervention and response to treatment.

RESULTS

Study summary and characteristics

Seven studies (two RCTs and five cohorts)[8–14] met the inclusion criteria. The article selection process is illustrated in Figure 1, and the extracted data are summarized in Table 1. A total of 382 participants were included, 28 of whom had non-TDBT with the homozygous beta-thalassemia (major thalassemia) genotype. To standardize the effect size comparison across studies, Cohen's d was used to convert the effect size values using data from the publications and supplements of each article. This systematic review included one, five, one, and one studies using thalidomide, HU, butyrate, and decitabine as HbF inducers, respectively.

Evidence quality and RoB assessment

Evidence quality and RoB appraisal were assessed using a previously described methodology, as shown in Supplementary Figure 1. Most studies have reported a moderate RoB. Based on the GRADE system, the evidence produced was deemed of very low to low quality (Table 2).

Quantitative analysis results

We calculated the SMD and standard error (SE) for Hb changes from four studies.[8,9,11,14] In the study by Bhattacharjee et al,[8] the data were divided into two different interventions (thalidomide and HU), whereas Yasara et al[9] divided the participants into responder and non-responder groups. The groups produced a pooled analysis using a random inverse variance model showing statistically insignificant results with high heterogeneity (SMD = 0.11; 95% confidence interval [CI] = −0.69 to 0.91; I^2 = 90%, P_{χ_2}<0.01). Further subgroup analysis with HU as the inducer remained insignificant, with high heterogeneity (SMD = −0.28; 95% CI = −1.06 to 0.51; I^2 = 91%, P_{χ_2}<0.01) (Figure 2).

The analysis of transfusion needs in the SMD and SE from four studies.[8,9,11,14] was found to decrease significantly, although heterogeneity remained high (SMD = −0.81; 95% CI = −1.37 to −0.26; I^2 = 79%, P_{χ_2}<0.01). Subgroup analysis for HU showed similar results (SMD = −0.80; 95% CI = −1.49 to −0.11; I^2 = 79%, P_{χ_2}<0.01) (Figure 3).

DISCUSSION

This study found that HbF inducers did not significantly alter Hb levels compared with the control treatment. Interestingly, several studies have reported that HU slightly decreases postoperative Hb levels.

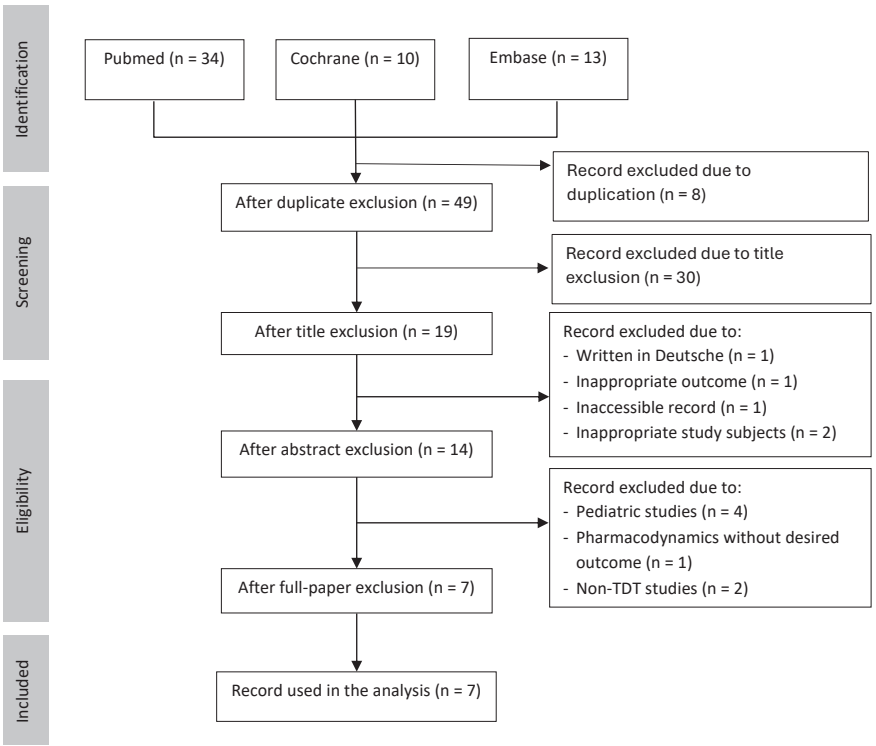

Figure 1. Flowchart of the record screening process

Table 1. Summary of records included

First author, year	Study characteristics		Subject characteristics			Intervention characteristics	Outcomes		
							Primary		Secondary
	Sample size; age (years), mean (SD)	Location	Genotype	Baseline Hb(g/dl), mean (SD)	Loss to follow-up, n (%)	Follow-up time	Agent & regiment (intervention arms)	Hematologic change (pre–post), SMD (95% CI)	Transfusion dynamics (pre–post), SMD (95% CI)	Safety profile
Bhattacharjee,[8] 2023	39; 26.9 (4.7)	Chandigarh, India	$\beta^0\beta^0$, $\beta^0\beta^+$ (severe), and Eβ heterozygous	9.03 (0.92)	6 (15)	6 months	Thalidomide 1 × 50 mg orally+ transfusion+ iron chelation (n = 14)	Hb change from baseline: 0.38 (−0.36 to 1.13) Ferritin difference from baseline: −0.25 (−0.99 to 0.48)	Volume per unit weight blood transfusion: Pre-: −0.74 (−1.50 to 0.02 Post-: −0.86 (−1.68 to −0.04)†	AE: constipation (7.1%), headache (14.3%), hyperbilirubinemia (7.1%), somnolence (78.5%), syncope (14.3%), and transaminitis (7.1%)
							HU 1 × 500 mg orally+ transfusion+ chelation (n = 13)	Hb change from baseline: 0.07 (−0.69 to 0.84) Ferritin difference from baseline: −0.01 (−0.78 to 0.75)	Volume per unit weight blood transfusion: Pre-: −0.34 (−1.11 to 0.43) Post-: −1.15 (−1.98 to −0.31)*†	AE: grade 1–2 abdominal pain (23.1%), grade 2 transaminitis (7.7%), grade 1 pruritis (15.4%)
							Control (transfusion+ chelation) (n = 12)	Hb change from baseline: 0.27 (−0.53 to 1.07) Ferritin difference from baseline: 0.19 (−0.60–0.99)	Volume per unit weight blood transfusion: Pre-: −0.41 (−1.22 to 0.39) Post-: 0 (0 to 0)	

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Table 1. (Continued)

First author, year	Study characteristics		Subject characteristics		Intervention characteristics			Outcomes		
								Primary		Secondary
	Sample size; age (years), mean (SD)	Location	Genotype	Baseline Hb(g/dl), mean (SD)	Loss to follow-up, n (%)	Follow-up time	Agent & regiment (intervention arms)	Hematologic change (pre–post), SMD (95% CI)	Transfusion dynamics (pre–post), SMD (95% CI)	Safety profile
Yasara,[9] 2022	60; 22.7	Kelaniya, Sri Lanka	IVS1-5(G→C)/ IVS1-5(G→C) (β0/ β0), IVS1-5(G→C)/ IVS1-1(G→A) (β0/ β0), IVS1-5(G→C)/ CD16(-C) (β0/β0), CD16(-C)/CD16(-C) (β0/β0),IVS1-1(G→A)/CD15(G→A) (β0/β0), CD8/9(+ G)/ CD8/9(+ G) (β0/β0), and IVS1-5(G→C)/ CD26 (β0/βE)	Baseline Hb: - HU: 8.1 (0.9) - Placebo: 8.0 (1.0) Baseline HbF: - HU: 4.2 (6.8) (51%) - Placebo: 5.4 (6.5) (67.5%)	12 (20)	12 months (6 months intervention+ 6 months post-intervention)	HU 10–20 mg/ kgBW/day+ transfusion+ iron chelation (n = 30)	HU responder: HbF increase >1.5% (n = 12 [44]%) Hb change from baseline: −0.03 (−0.70 to 0.63) HU non-responder: - HbF increase <1.5% (n = 15 [55%]) - 0.35 (−0.26 to 0.98) - 0.76 (0.21 to 1.32)†	Volume per unit weight blood transfusion 6 months intervention: - Pre-: −1.20 (−2.02 to −0.37)*‡ (compared to non-responder) - Post-: −0.88 (−1.58 to −0.17) Volume per unit weight blood transfusion 6 months post-intervention: - Pre-: −1.23 (−2.06 to −0.40)‡ (compared to non-responder) - Post-: −0.86 (−1.57 to −0.16)† Intervention: - Pre-: 1.20 (0.37 to 2.02)*‡ (compared to non-responder - Post-: 0.2 (0.39 to 0.86)† Post-intervention: - Pre-: 1.23 (0.40 to 2.06)‡ (compared to non-responder - Post-: 0.29 (−0.33 to 0.93)†	AE: headache (6.6%), leukopenia (3.3%), thrombocytopenia (3.3%), hyperpigmentation (3.3%), UTI (6.6%), nausea (3.3%), vomiting (3.3%), abdominal pain (3.3%), and eczematous rash (0%)
							Placebo+ transfusion+ iron chelation	Placebo (n = 30): 0.07 (−0.44 to 0.59)	NA	AE: headache (3.3%) and eczematous rash (3.3%)

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Table 1. (Continued)

First author, year	Study characteristics		Subject characteristics		Intervention characteristics			Outcomes		
								Primary		Secondary
	Sample size; age (years), mean (SD)	Location	Genotype	Baseline Hb(g/dl), mean (SD)	Loss to follow-up, n (%)	Follow-up time	Agent & regiment (intervention arms)	Hematologic change (pre–post), SMD (95% CI)	Transfusion dynamics (pre–post), SMD (95% CI)	Safety profile
Kalantri,[10] 2018	9; 26.88	Kolkata, India	CD26 (G → A) / IVS 1-5 (G→C) and phenotype severe	Baseline Hb: 6.85 (5.8–8.2) Baseline HbF: 17.67 (2.0–40.7)%	NA	3 months	Decitabine 0.2 mg/kgBW 2 times a week, subcutaneously	Peak Hb increase: 0.4 g/dl (p>0.05) Peak HbF increase (12 weeks):[§] 10.68 (5.6)%*	Significant change of pooled transfusion volume needs 74% transfusion volume decrease	AE (non-TDBT & TDBT): lower respiratory tract infection (10%), erosive gastritis (3.3%), minor articular pain (3.3%), dyspnea (3.3%), and hematological AEs (thrombocytopenia, leukopenia, and neutropenia) (0%)
Bordbar,[11] 2014	97; 20.27 (8.3)	Shiraz, Iran	Not stated, only clinical TDBT	Baseline Hb: 9.53 (1.1) Baseline HbF: 1.1 (0.3) (11.5%)	2 (2)	14 months (mean 7.72 [3.59])	HU 8, 10, or 14 mg/kgBW/day orally	Hb change from baseline: −1.33 (−1.65 to −1.02)* HbF change from baseline: 4.85 (4.29 to 5.42)* Serum ferritin: −0.14 (−0.43 to 0.14)*	Volume per unit weight blood transfusion at the end of follow-up: −1.33 (−1.64 to −1.01)* Transfusion interval: 2.60 (2.22 to 2.99)*	AE: transaminitis (16.5%), transient neutropenia (14.5%). Persistent neutropenia (excluded 2 patients)
de Paula,[12] 2003	4 TDBT and 7 NTDBT; 18.5 (2.29)	São Paulo, Brazil	β0β0/β0β+ (severe)	NA	NA	6–96 months	HU 10–20 mg/kgBW/day orally	NA	1 patient became transfusion independent, the rest are non-responder	AE: transient neutropenia (25%)

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Table 1. (Continued)

First author, year	Study characteristics		Subject characteristics		Intervention characteristics			Outcomes		
								Primary		Secondary
	Sample size; age (years), mean (SD)	Location	Genotype	Baseline Hb(g/dl), mean (SD)	Loss to follow-up, n (%)	Follow-up time	Agent & regiment (intervention arms)	Hematologic change (pre–post), SMD (95% CI)	Transfusion dynamics (pre–post), SMD (95% CI)	Safety profile
Yavarian,[13] 2004	133; 17.1 (5.2)	Bandar Abbas & Shiraz, Iran	β0β0/β0β+/ β+β+ phenotype (severe)	NA	2 (2)	60 months	HU 10–15 mg/ kgBW/day orally+ transfusion+iron chelation	HU responder (transfusion independent) (n = 81) Mean Hb during treatment: 10.3 (0.6) g/dl	Transfusion free	NA
								HU moderate responder (transfusion with 6 months or more of interval) (n = 31): 8.85 (0.4) g/dl	Transfusion with interval >6 months	
								HU non-responder (same level of dependency) (n = 21): 6.75 (0.5) g/dl	Same transfusion dependency	

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Table 1. (Continued)

First author, year	Study characteristics		Subject characteristics			Intervention characteristics		Outcomes		
								Primary		Secondary
	Sample size; age (years), mean (SD)	Location	Genotype	Baseline Hb(g/dl), mean (SD)	Loss to follow-up, n (%)	Follow-up time	Agent & regiment (intervention arms)	Hematologic change (pre–post), SMD (95% CI)	Transfusion dynamics (pre–post), SMD (95% CI)	Safety profile
Collins,[14] 1995	12; 29.54 (6.39)	Baltimore, Maryland, US (John Hopkins)	β0β0/βsβ0 phenotype (severe)	Baseline Hb: 6.71 (1.29) Baseline HbF: 37.42 (34.69)% Baseline HbF absolute: 2.73 (2.36)	NA	31–500 days (1–6 months)	Butyrate (sodium phenylbutyrate) 20 g/day orally + folic acid 1 mg/day	Butyrate responder (Hb increase >1 g/dl) (n = 4) Hb increase from baseline: 2.40 (0.58 to 4.22)* HbF increase from baseline: −0.21 (−1.19 to 0.79)% HbF absolute increase from baseline: 1.18 (−0.19 to 2.46) Hemolysis marker: - LDH difference from baseline: −1.33 (−2.69 to 0.11) - Indirect bilirubin difference from baseline: −1.06 (−2.28 to 0.25) Butyrate non-responder (Hb increase <1 g/dl) (n = 8): Hb increase from baseline: −1.02 (−0.12 to 1.57)* HbF increase from baseline: 0.81 (−0.07 to 1.67) HbF absolute increase from baseline: 0.75 (−0.12 to 1.57) Hemolysis marker: - LDH difference from baseline: −0.38 (−1.09 to 0.34) - Indirect bilirubin difference from baseline: −0.76 (−1.53 to 0.05)	NA	AE: high sodium diet related event (water retention and edema) (25%), nausea and GI symptoms post-administration (58.3%), malodorous body odor (25%), coagulation problem (25%)

AE=adverse event; BW=body weight; CI=confidence interval; GI=gastrointestinal; Hb=hemoglobin; HbE=hemoglobin E; HbF=hemoglobin F; HU=hydroxyurea; LDH=lactate dhydrogenase; NA=not available; NTDBT=non-transfusion-dependent beta-thalassemia; RR=risk ratio; SD=standard deviation; SMD=standardized mean difference; sTfR=soluble transferrin receptor; TDBT=transfusion-dependent beta-thalassemia

*$p<0.05$; †compared to control; ‡compared to other non-control arms; §SMD cannot be computed

Table 2. GRADE rating for evidence quality

Evidence	Measurement (effect size)	N	Effect size	GRADE assessment				Grade	Importance
				Risk of bias	Inconsistency	Imprecision	Indirectness		
Hematologic change									
Pooled analysis	Hb pre–post intervention (SMD)	4	0.11 (−0.69; −0.91); I^2 = 90%	–	–	–	+	+ – – – Very low	Critical
HU		3	−0.28 (−1.06; −0.51); I^2 = 90%	+	–	–	+	+ + – – Low	High
Transfusion need									
Pooled analysis	Transfusion volume/ body weight (SMD)	4	−0.81 (−1.37; −0.26); I^2 = 79%	–	–	–	+	+ – – – Very low	Critical
HU		3	−0.80 (−1.49; −0.11); I^2 = 84%	+	–	–	+	+ + – – Low	High

GRADE=grading of recommendations, assessment, development, and evaluation; HU=hydroxyurea; SMD=standardized mean difference

However, the high heterogeneity of the analysis and broad CIs suggested that the resultant Hb changes were both diverse and most likely insignificant, largely depending on the genotypes, phenotypic responses, and the variety of regimens between trials. Conversely, the inducers significantly reduced transfusion requirements, particularly in the HU responder-only group. Notably, most studies have reported substantial effects on Hb levels and changes in transfusion dynamics within 3 months of HU therapy. A decitabine study reported a reduction in total transfusion volume by up to 74%.[10] Similarly, BU has been shown to reduce the transfusion number in some patients, while also significantly increasing Hb levels, as reported by Collins et al.[14] Evidence compiled in this review clearly supports the beneficial effects of inducers in adult TDBT patients, especially HU, in improving transfusion dynamics.

Responses to HbF inducers vary across patients, with studies classifying participants into responders and non-responders based on hematologic parameters (such as HbF increase) and transfusion reduction volume. The difference determines the magnitude of the intervention effect, where responders benefit more than non-responders do. For example, Yasara et al[9] observed a significant change in transfusion volume among the responder arm compared to non-responders (SMD = −1.20 [−2.02 to −0.37], p = 0.005), and a responder arm *versus* placebo arm (SMD = −0.88 [−1.58 to −0.17], p = 0.015). Yavarian et al[13] even observed that the responder group maintained Hb ≥9.5 g/dl with no transfusion required, while moderate responders decreased their transfusion interval for up to ≥6 months, and non-responders continued requiring transfusions at the same interval with Hb levels ≤7.5 g/dl. Response variability was wide. In a small cohort report, a minority of patients achieved transfusion independence by approximately 9 months post-intervention, whereas others did not respond.

The high heterogeneity in our study may be attributed to several factors, including differences in patient genotype, study protocol, follow-up duration, and small sample size. Yavarian et al[13] highlighted the influence of genetic factors relevant to HbF induction using HU, with *Xmn1* polymorphism (T homozygosity), β-globulin framework 2, HbE (Cd26), and IVSII-1 (G>A) alleles positively linked to increased HbF level of >1.5 in 6 months post-intervention. Conversely, the IVSI-5 (G>C) genotype was identified as a negative predictor. For comparison, individuals with *Xmn1* (C→T) polymorphism at −158 upstream of the *γG-globin* gene are five times more likely to respond to HU compared to patients without this polymorphism.[13] While molecular profiling could help predict response, monitoring hematologic profile and transfusion dynamics remains the most practical approach to determine drug response. The mechanism behind the genetic dependency of the response remains largely unknown, though the −158 *Xmn1* polymorphism (C→T) is thought to promote γG-globin expression, with inducers further amplifying this phenotype, resulting in higher HbF levels.

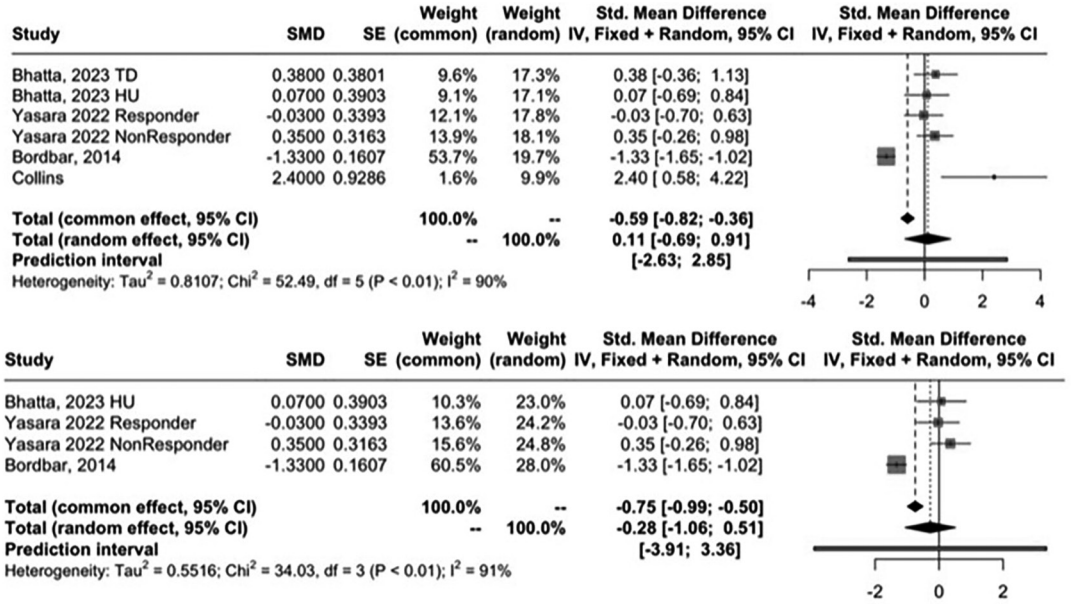

Figure 2. Forest plot of Hb change of the included studies: (a) pooled analysis of Hb change post-intervention; (b) subgroup analysis with HU as the inducer. CI=confidence interval; Hb=hemoglobin; HU=hydroxyurea; IV=inverse variance; SE=standard error; SMD=standardized mean difference; TD=thalidomide

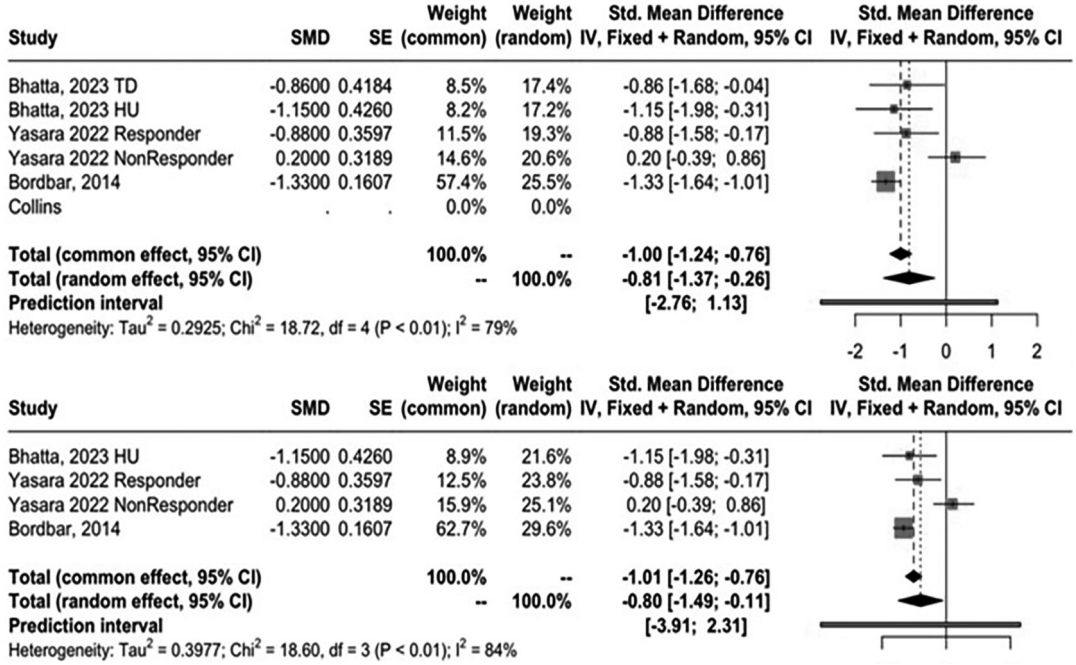

Figure 3. Forest plot of the transfusion dynamics change of the included studies: (a) pooled analysis of transfusion dynamics change; (b) subgroup analysis with HU as the inducer. CI=confidence interval; HU=hydroxyurea; IV=inverse variance; SE=standard error; SMD=standardized mean difference

Beyond reducing transfusion needs, HbF induction also consistently showed significant decreases in erythropoietic stress and hemolytic activity across all studies that reported it. The decline in ferritin levels indicates the amelioration of iron overload. The reduction in soluble transferrin receptor levels indicates erythropoiesis stress, suggesting that the intervention helps reduce ineffective erythropoiesis, which is one of the pivotal pathophysiologies of beta-thalassemia. This can reduce the risk of extramedullary erythropoiesis and increase iron retention. These benefits could help patients and potentially reduce

their dependence on iron chelation therapy. However, the exact effect of HbF inducers on the need for iron chelation agents remains unclear, as most studies have shown no significant change in ferritin levels, except that by Bordbar et al.[11]

The most common side effects of HbF-inducing agents are liver-related disorders, such as pruritus, hyperbilirubinemia, and transaminitis (increased transaminase enzymes indicating hepatocyte cell damage). Myelosuppression, characterized by neutropenia, thrombocytopenia, and leukopenia, also frequently improves upon discontinuation of the agent. Other effects include neurological symptoms, such as somnolence, syncope, and headache, and gastrointestinal symptoms, including vomiting, nausea, abdominal pain, gastric erosion, and constipation.[15] The most common HbF-related AEs were mild hematological conditions (24.1%), transaminitis (21.6%), mild neurological conditions (20.4%), gastrointestinal-related conditions (20.4%), and others/unspecified (13.2%). Some studies have reported atypical symptoms, including worsened body odor and edema, due to high sodium intake (especially with butyrate derivatives), whereas the side effects of other induction agents are relatively similar.

The side effects of HbF inducers can be attributed to their mechanisms, including inhibition of cell proliferation through changes in gene expression, suppression of deoxyribonucleoside production and cell cycle S-phase inhibition (HU), modulation of histone deacetylase activity (butyrate and decitabine), and suppression of nuclear factor kappa B (thalidomide). These mechanisms lead to epigenetic changes that promote HbF or γ-globin activation, which are typically suppressed in adults. Additionally, thalidomide and HU trigger reactive oxygen species production in myeloblastic cells, causing cytotoxic mechanisms that increase γ-globulin gene expression via stress-mediated cell signaling. Owing to these mechanisms, high expansion rates, especially in myeloblastic cells, experience the highest impact and lead to myelosuppression.[16,17] However, this range of AEs is dose-dependent, and resolution always occurs after dose discontinuation. Furthermore, studies by Bhattacharjee et al,[8] Kalantri et al,[10] and Yasara et al[9] confirmed that AEs were relatively mild and tolerable for most participants, even for those who continuously used the agent even after the study follow-up period ended, indicating that AEs are highly individual-dependent and that those who respond well can continue the intervention for an extended period.

Data from online drug stalls and distributors indicate the price ranges of several available HbF-inducing drugs in Indonesia. HU costs approximately USD 6.10–12.20 for 100 tablets (500 mg each), decitabine (Dacogen) is USD 700 per 20 ml vial, and thalidomide (Thalix) is USD 117.20 for 30 tablets (100 mg each), while butyrate is not available in Indonesia as it is largely irrelevant to current treatment regimens. Considering its availability, cost, and efficacy, HU is the most affordable and viable option, costing USD 0.06 per day (500 mg daily oral dose), followed by thalidomide at USD 2.00 per day (50 mg daily oral dose); however, there is weaker evidence. Therefore, HU is the most feasible choice in Indonesia, with a daily oral dose of 500 mg/day (15–17 mg/kg body weight/day). Therefore, using HU as an adjuvant therapy, rather than relying specifically on blood transfusions and iron chelation, can offer economic advantages at both the individual and national levels.

Thalassemia is a costly condition requiring lifelong treatment. A review by Wahidayat et al[2] estimated that the monthly expense for an adult patient with thalassemia major at Cipto Mangunkusumo Hospital was approximately USD 1,330.50. These included routine packed red blood cell (RBC) transfusion and pre-transfusion protocols (USD 291.40/patient per month), iron chelation therapy (USD 840–1,134/patient per month), and routine consultation with subspecialists (USD 52.10/month).

Implementing HU as an inducer for patients undergoing TDBT imposes an upfront cost of USD 3.70/patient per month. Based on our results, HU is expected to reduce the average transfusion needs by 20–30%, leading to a direct cost reduction of USD 60.00/patient per month from transfusion only. Considering that approximately 10,000 patients with TDBT are covered by the Indonesian National Health Insurance, this would equate to an estimated USD 600,000 in monthly cost reduction or approximately USD 7.2 million annually of direct cost averted from blood transfusion.[18] Notably, the government would spend approximately USD 444,000 for the total annual implementation cost, bringing net annual cost savings of USD 6,756,000 per year. Although the impact of HbF inducers on iron chelation therapy remains unclear, decreasing transfusion frequency may help lower iron

overload; importantly, this would reduce the intensity of the iron chelation regimen, further decreasing the overall economic burden, as iron chelation therapy accounts for most of the costs.

Wahidayat et al[2] reported that hemovigilance and therapy compliance were higher in Indonesia than in other countries. However, these strengths are sometimes not accompanied by a stable supply of treatment modalities such as transfusion and iron chelation. Fluctuations in demand and supply frequently lead Indonesian physicians to rely on suboptimal solutions, such as treatment microdosing, to meet the growing demand.[2] This calls for a new solution that may alleviate the ever-growing request for treating TDBT patients.

In Indonesia, standard thalassemia treatment (iron chelation and transfusion) is covered by the BPJS. However, as it is categorized as a catastrophic disease, it requires an annual budget of more than IDR 580 billion or USD 35.5 million, despite its comparatively low prevalence.[18] Moreover, limited infrastructure for blood donation and other blood products creates a highly volatile population among patients with thalassemia. Using HU as an adjuvant reduces transfusion needs, with an estimated 30–50% of HU users experiencing this reduction or being responders. This is supported by pediatric research by Sari et al,[19] who reported a 60% reduction in transfusion needs in the pediatric HU group, indicating a positive response to HU use in Indonesia.

Indonesian patients undergoing TDBT possess unfavorable characteristics for the use of inducers. The homozygous IVS 1–5 (G>C) mutation, a phenotypically high HbF, is the dominant genotype in Indonesia. This is followed by IVS 1–5/Cd26 genotype (thal β/HbE genotype), which usually responds well to therapy, and a low frequency of homogenous *Xmn1* polymorphism.[20]

Although individuals with homozygous IVS 1–5 phenotypically possess high HbF levels, they remain anemic. The authors argued that this is due to the better survivability of HbF-containing RBCs compared to that of faulty HbA-containing RBCs. In contrast, the compensatory increase in hematopoiesis cannot meet the body's needs due to ineffective erythropoiesis. As a result, HbF-containing RBCs dominate the RBC population despite having a low or inadequate quantity compared to the ineffectively formed HbA-containing RBCs, leading to persistent anemia despite high HbF levels.

Despite the unfavorable characteristics of Indonesian patients undergoing TDBT, HbF inducers may still boost erythropoiesis efficiency. Therefore, rather than relying solely on patient genotypes, a 6-month trial with HU at 10–15 mg/kg BW/day is recommended in clinical settings to determine a patient's phenotypic response. This approach minimizes the need for molecular profiling, allowing physicians to tailor the dosage and regimen based on the observed Hb increase and transfusion intervals. This study also suggests a strong need for further research in Indonesia to appraise the feasibility of inducers in curbing transfusion needs among pediatric and adult patients with TDBT.

A limitation of this study is the variation in design, effect size, and characteristics of the selected research. These studies, published between 1995 and 2022, differed significantly in terms of their methodologies and statistical approaches. Most research consisted of non-RCTs, which are the gold standard for interventional research and provide a high level of evidence. Additionally, some studies, such as those by Bordbar et al[11] and Collins et al[14] did not include clear follow-up limits, resulting in high dropout rates that were not explicitly mentioned. Moreover, the authors strongly recommend the inclusion of genotype data in future reviews on thalassemia. Given the high correlation between disease phenotype, intervention response, and the applicability of the results, certain genotypes tended to cluster within populations.

Despite these limitations, in this meta-analysis, the calculation and standardization of the effect size of the SMD were the most essential data. Moreover, the available data closely aligned with the target population, namely adult patients with TDBT beta, enhancing its relevance to clinical practice. This distinction is crucial, considering the differences in HbF physiology between adult and child patients, suggesting separate study characteristics.

In conclusion, HbF-inducing agents are highly effective in reducing the need for transfusion and have high validity, particularly for HU. However, their effects on other important laboratory profiles, such as Hb levels, erythrocyte counts, indices, and iron profiles, remain unclear because of heterogeneous study results. Given their cost-effectiveness, efficacy, and safety profile, HbF inducers can be considered viable adjuvant therapy options for patients with transfusion-dependent thalassemia. Nonetheless, more research

is needed to evaluate the response in the Indonesian population and to explore HbF inducers beyond HU because of the limited number and quality of evidence for alternative induction agents.

HbF-inducing agents, especially HU, are recommended as adjuvants to reduce the volume and interval between transfusions. Moreover, in patients with post-transfusion immunological reactions or in those contraindicated for transfusion, HbF induction agents can be used to alleviate erythropoietic stress and reduce the impact of anemia. The recommended dose of HU is 1 × 500 mg orally, with adjustments based on BW (10–20 mg/kg BW/day). In the case of AEs, particularly myelosuppression or unbearable gastrointestinal symptoms, the agent can be temporarily discontinued and gradually reintroduced.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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