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Proposed Framework

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Thalidomide in Transfusion-Dependent Beta-Thalassaemia in Pakistan: A Proposed Framework for Safe Prescribing, Risk-Stratified Monitoring, and Pharmacovigilance

Abstract

Background. Transfusion-dependent beta-thalassaemia (TDT) kills children in Pakistan. Mortality from iron overload complications, cardiac siderosis, and panhypopituitarism is common before adulthood in settings where access to regular transfusion and chelation is poor. In this context, thalidomide has been adopted at multiple centres as an off-label fetal haemoglobin (HbF) inducer to reduce transfusion dependence. It is being used, frequently, without patient registration, without any pregnancy risk assessment, and without pharmacovigilance reporting to the Drug Regulatory Authority of Pakistan (DRAP).

Clinical Context. Unlike Western populations or well-resourced Asian thalassaemia centres, the majority of female TDT patients in Pakistan never reach menarche. Iron-overload-driven hypogonadotrophic hypogonadism is documented in over 80% of Pakistani TDT patients. A framework that applies blanket pregnancy prevention rules to this population is both clinically inappropriate and practically undeliverable in remote settings. It also diverts attention from the patients who genuinely need those protections.

Objectives. To review the evidence for thalidomide in TDT, document its known risks in the Pakistani context, and propose a practical risk-stratified prescribing and monitoring framework adapted from the US S.T.E.P.S. programme.

Proposed Framework. Five components are proposed: (1) prescriber and centre registration; (2) risk-stratified reproductive assessment with targeted pregnancy prevention for those who actually need it; (3) structured haematological, neurological, and endocrine monitoring; (4) response assessment at six months; and (5) compulsory adverse event reporting through DRAP.

Conclusions. Thalidomide offers real benefit to a population with few alternatives. The teratogenic risk is real but applies to a minority of patients in Pakistan's TDT population. A framework that ignores the endocrine reality of Pakistani TDT patients protects no one and will not be followed. One that is honest about who needs protecting, and how, might be.

Keywords: thalidomide; beta-thalassaemia; transfusion-dependent thalassaemia, hypogonadism; iron overload; teratogenicity; pharmacovigilance; S.T.E.P.S.; DRAP; HbF; pan hypopituitarism

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Introduction

In Pakistan, thalassaemia is not a managed chronic condition for most patients. It is a disease that shortens childhood. Pakistan has one of the highest TDT burdens in the world, with an estimated 5,000 to 9,000 severely affected births annually and a carrier prevalence of 3% to 8% across different regions.¹In theory, the standard of care is lifelong regular red cell transfusion with iron chelation. In practice, outside a small number of well-resourced urban centres, transfusion is irregular, chelation is often absent or inadequate, and access to stem cell transplantation, the only established cure, is severely limited by donor availability, cost, and institutional capacity.

The consequences are predictable. Iron accumulates. The anterior pituitary is particularly sensitive to iron deposition, and progressive disruption of gonadotrophin secretion leads to hypogonadotrophic hypogonadism, growth failure, and absent or arrested puberty. A multicentre Pakistani study of 280 TDT patients found hypogonadism in 82%, stunting in 69%, hypoparathyroidism in 40%, and hypothyroidism in 30%.¹¹Many children in remote settings die from cardiac siderosis or other complications of iron overload before they reach adulthood.

It is in this setting that thalidomide is being used. As an off-label fetal haemoglobin (HbF) inducer, it offers the possibility of reducing transfusion dependence in patients refractory to hydroxyurea,² without the infrastructure required for transplantation. The drug is

now being prescribed at multiple Pakistani thalassaemia centres. In the majority of those centres, it is being prescribed without patient registration, without any assessment of who is genuinely at reproductive risk from thalidomide's teratogenicity, and without pharmacovigilance reporting to DRAP.

The framework described in this paper is an attempt to address that. It draws on the US S.T.E.P.S. programme, the access and monitoring structure mandated by the FDA as a condition of thalidomide's 1998 re-approval,⁵ and on the EMA Summary of Product Characteristics (SmPC) for Thalidomide BMS.⁸ But it departs from both in one important respect. The S.T.E.P.S. programme was designed for a population in which women of childbearing age who are prescribed thalidomide are, by default, capable of pregnancy. That default does not hold in Pakistan's TDT population. A framework that treats every female TDT patient as a woman requiring intensive pregnancy surveillance is not only clinically wrong, it is a framework that will not be followed in the settings where it is most needed. This paper proposes a risk-stratified approach instead.

The Pakistani TDT Population: What the Evidence Shows

Before discussing thalidomide's efficacy or its risks, it is worth being clear about who is actually being treated. Most TDT patients who receive thalidomide in Pakistan are children or young adults who have been inadequately transfused and inadequately chelated, often for years. The endocrine consequences of that iron burden are not incidental. They define the patient's physiology. Iron deposition on gonadotroph cells of the anterior pituitary disrupts FSH and LH secretion. The damage is progressive. Even when intensive chelation is started, it often cannot fully reverse it.¹² The result is a spectrum that runs from delayed puberty through primary amenorrhoea to complete panhypopituitarism, depending on when iron overload started, how severe it was, and how late chelation began.

The scale of this in Pakistan is documented. Ehsan and colleagues at Aga Khan University, in a multicentre retrospective study of 280 Pakistani TDT patients, found hypogonadism in 82% and stunting in 69%.¹¹ These figures are substantially higher than those reported from well-chelated Mediterranean cohorts, where hypogonadotrophic hypogonadism is reported in

approximately 32% of patients.¹³ The difference reflects the reality of inadequate chelation in a resource-limited setting, not a different disease.

The clinical implication is direct. Most female TDT patients in Pakistan, particularly those from remote or under-resourced settings, have never menstruated. They are not ovulating. The risk that thalidomide causes foetal malformations in these patients is not zero, because gonadal function can occasionally recover with improved chelation, but it is fundamentally different from the risk in a normally cycling woman.¹²

A framework that applies the same mandatory monthly pregnancy testing to an amenorrhoeic 16-year-old with a ferritin of 8,000 micrograms per litre and undetectable oestradiol as to a 28-year-old woman with regular cycles is not a safety framework. It is a protocol that will be ignored, and in being ignored will distract attention from the patients who genuinely need protecting.

At the same time, some female TDT patients in Pakistan are actively menstruating. Patients receiving good transfusion and chelation from tertiary urban centres may have intact gonadal function. Patients from better-resourced families may have recovered pituitary function. These patients are capable of pregnancy. They need the full protection the S.T.E.P.S. programme was designed to provide. The task is to identify them and direct that protection accurately.

Thalidomide in TDT: Clinical Evidence

Thalidomide reactivates gamma-globin gene expression through direct regulation of haemoglobin transcription, slowing erythroid maturation and increasing the proportion of immature erythroid cells with higher HbF content.⁴ The mechanism differs from hydroxyurea, which acts through cytotoxic stress on erythroid progenitors. The combination of the two drugs has been studied and may have additive effects on HbF.²

The key clinical studies are summarised in Table 1. The most substantial Pakistani evidence comes from the Thal-Thalido study, a single-arm non-randomized trial of 532 TDT patients refractory to hydroxyurea, followed for 30 months in Peshawar.³ The most rigorous evidence synthesis is the 2026 systematic review and meta-analysis by Li and colleagues, encompassing 26 studies and 2,422 patients with GRADE evaluation.⁶

Table I: Summary of key clinical studies of thalidomide in transfusion-dependent beta-thalassaemia (TDT).

Study (Year)	Design	n	Setting	Key efficacy and safety outcomes
Ali et al. (Thal-Thalido), 2023 ³	Single-arm, non-randomised, 30 months	532	Peshawar, Pakistan	ORR 76.7%; mean Hb rise 2.0 g/dL at 30 months ($p \leq 0.001$); serious adverse events: CVA 0.38%, PVT 0.38%; mild AEs in 9.8%
Bhattacharjee et al., 2024 ²	Single-arm prospective trial	41	Kolkata, India	ORR 63.4%; 46.3% achieved transfusion independence; improved QoL in responders; no significant adverse reactions
Li et al. (SR and MA), 2026 ⁶	Systematic review, meta-analysis, GRADE, 26 studies	2,422	Multi-national	MRR 62.91%; ORR 75.07%; mean Hb rise 1.94 g/dL; mean HbF rise 39.21%; ADE rate 4.65 per 100 person-months; moderate certainty for Hb and HbF outcomes

ORR = overall response rate; MRR = major response rate; SR = systematic review; MA = meta-analysis; HbF = fetal haemoglobin; QoL = quality of life; ADE = adverse drug event; CVA = cerebrovascular accident; PVT = portal vein thrombosis.

Two points require frank acknowledgement. First, thalidomide holds no marketing authorisation from the EMA or FDA for TDT. All use in this context is off-label. Second, the evidence base, while encouraging, carries moderate certainty at best. The 2026 meta-analysis rated certainty as moderate for haemoglobin and HbF outcomes and very low for some secondary outcomes.⁶ Large, well-designed randomised controlled trials with long-term safety data are still lacking. The absence of that evidence does not prohibit use in a population with

few alternatives, but it makes systematic monitoring and reporting more important, not less.

Known Risks

Table II: Summarizes the adverse effect profile from the EMA SmPC and TDT trial data. The four risks that require most careful management in Pakistan are discussed below

Teratogenicity

This is the risk that defines thalidomide's history and the reason it requires a safety programme. The EMA SmPC states that thalidomide induces severe and life-threatening birth defects at approximately 30%

Table II: Adverse effects of thalidomide: frequency from the EMA Summary of Product Characteristics

Adverse effect	Frequency (SmPC) ^a	Incidence in TDT trials	Clinical notes
Teratogenicity	Contraindicated in pregnancy	Not quantifiable; pregnancies not permitted in trials	~30% risk of severe birth defects per EMA SmPC; ^a critical window days 34-50 of gestation; single 100 mg dose sufficient to cause malformations; ⁵ see risk stratification Table III
Peripheral neuropathy	Very common (>1 in 10)	Paraesthesia 0.8% in Thal-Thalido ³	May be irreversible after discontinuation; ⁸ risk increases with cumulative dose; dose modification by NCI-CTCAE grade per Table 4
VTE / arterial events	Uncommon to common, regimen-dependent	CVA 0.38%; PVT 0.38% in Thal-Thalido ³	TDT is independently hypercoagulable; post-splenectomy highest risk; VTE prophylaxis decisions must be individualised ³⁹
Neutropenia	Very common (>1 in 10)	1.1% in Thal-Thalido ³	Monitor FBC monthly; dose reduce or interrupt for Grade 3-4
Somnolence / dizziness	Very common (>1 in 10)	Not formally graded in TDT trials	Administer at bedtime; counsel on driving and machinery ⁸
Constipation	Very common (>1 in 10)	6.2% in Thal-Thalido ³	Most frequent adverse event reported; manage symptomatically
Hypothyroidism	Uncommon	Not separately reported in TDT trials	Also an independent complication of iron overload; monitor TSH at baseline, 3 months, then 6-monthly ⁸
Serious skin reactions	Common; SJS/TEN post-marketing	Skin rash 0.9% in Thal-Thalido ³	Discontinue immediately if SJS or TEN suspected; report to DRAP within 24 hours
Bradycardia	Uncommon	Not reported in TDT trials	Monitor heart rate; caution with negatively chronotropic drugs ⁸

(SmPC)^a and incidence in TDT clinical trials. VTE = venous thromboembolism; CVA = cerebrovascular accident; PVT = portal vein thrombosis; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ADL = activities of daily living; DRAP = Drug Regulatory Authority of Pakistan.

Superscript numbers refer to the reference list.

frequency.⁸ The range of defects includes amelia and phocomelia, microtia, ocular abnormalities, congenital heart disease, and renal malformations. A single 100 mg dose taken between days 34 and 50 of gestation has been documented to cause malformations.⁵ There is no known safe period during pregnancy.⁵ The original thalidomide disaster resulted in approximately 12,000 affected births before the drug was withdrawn globally in 1961.

In Pakistan's TDT population, the absolute risk of fetal exposure during thalidomide treatment is substantially lower than in Western populations, precisely because most female patients are amenorrhoeic from iron overload. This does not mean the risk is absent. It means it applies to a defined subgroup that can be identified, and it is that subgroup which must receive the full protection of the consent and contraception requirements described in Component 2 of this framework.

Peripheral Neuropathy

The EMA SmPC classifies peripheral neuropathy as very common, affecting more than one in ten patients, predominantly sensory and starting distally.⁸ A critical point is that it may be irreversible after the drug is stopped.^{8,9} Risk increases with cumulative dose. In the Thal-Thalido study, paraesthesia was recorded in 0.8% of 532 patients over 30 months,³ which probably reflects both the lower TDT dosing range (2 to 5 mg/kg/day versus 200 to 400 mg/day in myeloma regimens) and under-reporting in the absence of formal neurological assessment tools. Peripheral neuropathy also occurs independently in thalassaemia patients from iron overload and nutritional deficiencies, which may complicate attribution and grading in Pakistani clinics without neurophysiology access.

Venous Thromboembolism and Arterial Events

Thalidomide is prothrombotic. VTE rates up to 15% have been documented with thalidomide combined with dexamethasone in myeloma.^{8,9} TDT itself is a hypercoagulable state, driven by ineffective erythropoiesis, chronic haemolysis, platelet activation, and endothelial dysfunction. Splenectomised patients carry additional risk. In the Thal-Thalido study, portal vein thrombosis occurred in two patients and cerebrovascular accident in two patients, each 0.38% of the cohort, all

resolving after drug cessation and anticoagulation.³ Risk stratification at baseline, attention to post-splenectomy status, and a low threshold for clinical assessment of possible VTE are warranted in this population.

Iron Overload and Endocrine Complications

Iron overload is not merely a background feature of this patient group. It is the defining pathology that shapes every risk assessment in this framework. The anterior pituitary, thyroid, parathyroid glands, and pancreatic beta cells are all susceptible to iron deposition.^{13,12} In the Pakistani TDT population, hypogonadism (82%), stunting (69%), hypoparathyroidism (40%), and hypothyroidism (30%) have all been documented at rates substantially higher than those reported from well-chelated European cohorts.¹¹ Thalidomide does not worsen these complications directly, but clinicians must assess and document endocrine status at baseline and monitor it regularly, both because it determines the reproductive risk category (see Component 2 and Table 3) and because the drug's tolerability and the patient's clinical trajectory depend on it.

A Proposed Framework for Safe Prescribing

The framework presented here is adapted from the S.T.E.P.S. programme⁵ and the EMA SmPC for Thalidomide BMS,⁸ but is shaped by the clinical realities of TDT in Pakistan. It has five components. A national DRAP-administered registry for thalidomide in TDT does not currently exist in Pakistan. Until one is established, these components should be adopted at institutional level by every centre prescribing this drug for TDT.

Component 1: Prescriber and Centre Registration

Every clinician who prescribes thalidomide for TDT must sign a written prescriber agreement before writing any prescription. This agreement confirms that the prescriber has read this framework, accepts responsibility for baseline assessment, patient registration, monitoring, and adverse event reporting, and will limit each prescription to 28 days with no repeat dispensing without a documented clinical review.

Every patient must be registered in the centre's institutional thalidomide register before the first dispensing. This register must capture: diagnosis and genotype; current transfusion frequency; iron chelation status and current ferritin; reproductive status as

assessed by the framework in Component 2; baseline investigations; date of consent; and prescriber name. Dispensing pharmacies must verify registration before each supply and must not dispense to unregistered patients.

Component 2: Reproductive Risk Assessment and Targeted Pregnancy Prevention

This is the component where most existing frameworks fail in the Pakistani context. Importing Western WOCBP rules wholesale into a population where the majority of female patients are amenorrhoeic from iron-overload-driven hypogonadism is clinically inaccurate, logistically undeliverable in remote areas, and ultimately counterproductive because it undermines confidence in the entire framework.

The correct approach is to stratify reproductive risk at baseline using the patient's menstrual history, pubertal

status, and hormonal profile, and to direct intensive pregnancy prevention measures only to those who are genuinely at risk. Table III specifies the recommended approach by patient group.

The key practical points of this stratification are four. First, pre-pubertal children require general consent and explanation, not pregnancy testing. Second, post-pubertal females who have never menstruated and who have evidence of hypogonadotrophic hypogonadism require a single baseline test and reassessment at six months and annually, not monthly testing. Third, any female patient in whom menstrual cycles are established, however irregularly, must be treated as WOCBP and receive the full EMA SmPC contraception and testing protocol. Fourth, reproductive status is not fixed in this population. Improved chelation can partially restore gonadotrophin secretion.¹² Any patient whose reproductive status changes must be reclassified

Table III: Risk-stratified reproductive assessment and pregnancy prevention by patient group.

Patient group	Reproductive status and rationale	Recommended action
Pre-pubertal children (male and female)	No reproductive risk. The majority of TDT patients in Pakistan commence thalidomide before puberty. Iron-overload-driven gonadotrophin disruption begins in childhood.	General consent; no pregnancy testing; explain drug risks to parent/guardian
Female, no menarche, post-pubertal age	Primary amenorrhoea from hypogonadotrophic hypogonadism or panhypopituitarism secondary to iron overload. In Pakistani TDT cohorts, hypogonadism prevalence exceeds 80%. ¹⁰ These patients are not ovulating.	Document menstrual status clearly. Single baseline pregnancy test. Reassess at 6 months and annually. No mandatory monthly testing unless menses established.
Female, secondary amenorrhoea	Previously menstruating; cycle ceased, likely due to progressive iron-overload gonadotoxicity. Confirm hypogonadotrophic hypogonadism with FSH, LH, and oestradiol before classifying.	Hormonal profile to confirm anovulatory status. Single pregnancy test at baseline. Reassess every 6 months. If LH/FSH recover (e.g. after chelation improvement), upgrade to standard WOCBP monitoring.
Female with active menstrual cycles (WOCBP)	Actively ovulating. True WOCBP. Applies to minority in poorly chelated Pakistani settings but must be identified and protected.	Full EMA SmPC protocol: two simultaneous contraceptive methods; negative pregnancy test (<50 mIU/mL) before first dose; weekly testing month 1; monthly or fortnightly thereafter per cycle regularity; 4 weeks after stopping
Female, post-menopausal or irreversible surgical sterilisation	No reproductive risk.	General consent; no pregnancy testing required
Male patients	Thalidomide excretion in semen is unquantified. Cannot be presumed safe.	Condom use with any WOCBP partner throughout therapy and 4 weeks after stopping. No blood or semen donation during therapy.

This framework reflects the endocrine reality of the Pakistani TDT population, in which iron-overload-driven hypogonadotrophic hypogonadism affects the majority of female patients. WOCBP = women of childbearing potential; FSH = follicle-stimulating hormone; LH = luteinising hormone; EMA SmPC = European Medicines Agency Summary of Product Characteristics.

* Where LH and FSH testing is unavailable, clinical assessment (presence or absence of secondary sexual characteristics, menstrual history, pubertal staging) should be documented and reviewed at 6 months.

promptly.

For male patients, the same rule applies regardless of context: condoms must be used during intercourse with any WOCBP partner throughout therapy and for four weeks after stopping.⁵ Thalidomide excretion in semen has not been quantified and the risk to a fetus cannot be excluded. Males must not donate blood or semen during treatment.⁵

Informed consent must be documented for every patient before the first dispensing, conducted in the patient's preferred language, and retained in the patient record. For paediatric patients, consent is obtained from the parent or guardian with age-appropriate explanation to the child. Consent must cover the drug's off-label status, the risk of peripheral neuropathy, thrombosis, and teratogenicity with its implications for the patient's reproductive risk category, the monitoring requirements, and the reporting process if problems arise.

Component 3: Structured Clinical Monitoring

Table IV specifies the monitoring schedule. Two aspects deserve specific comment for the Pakistani context.

Neurological monitoring is the parameter most likely to be neglected in resource-limited settings. A formal neurological assessment at baseline, using a structured symptom questionnaire covering lower limb sensation,

balance, and pain, takes five minutes. Repeating it at every clinic visit identifies early neuropathy before it becomes irreversible. This matters particularly in Pakistan because peripheral neuropathy from iron overload and nutritional deficiency may already be present at baseline, and any new or worsening symptoms after thalidomide starts must be attributed and graded carefully. Dose modification follows NCI-CTCAE grading as set out in Table V.

Table V: Dose modification guidance for thalidomide-induced peripheral neuropathy.

NCI-CTCAE Grade	Description	Recommended action
Grade 1	Asymptomatic; clinical or diagnostic findings only	Continue current dose; document and review at next visit
Grade 2	Moderate symptoms; limiting instrumental ADL	Reduce dose by 50%; reassess at 4 weeks; consider neurology review
Grade 3	Severe symptoms; limiting self-care ADL	Withhold immediately; formal neurology assessment; consider permanent discontinuation
Grade 4	Life-threatening; urgent intervention required	Permanently discontinue; urgent neurology referral; report to DRAP within 15 days

based on NCI-CTCAE grading and adapted from the EMA Summary of Product Characteristics.⁸ NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ADL = activities of daily living; DRAP = Drug Regulatory Authority of Pakistan.

Table IV: Recommended monitoring schedule for patients receiving thalidomide for TDT.

Parameter	Baseline	Months 1-3	Month 4 onwards
Full blood count with differential	Yes	Monthly	Every 3 months
Serum ferritin	Yes	Monthly	Every 3 months
Liver function tests (ALT, AST, bilirubin)	Yes	Monthly	Every 3 months
Renal function (urea, creatinine, eGFR)	Yes	Monthly	Every 3 months
Serum LDH and uric acid	Yes	Monthly	Every 3 months
Haemoglobin level	Yes	Monthly	Monthly
HbF level	Yes	At 3 months	Every 3 months
Thyroid function (TSH, free T4)	Yes	At 3 months	Every 6 months
Neurological symptom assessment	Yes (formal)	Every clinic visit	Every clinic visit (min. 3-monthly)
Thrombosis risk assessment	Yes (documented)	Symptom review each visit	Symptom review each visit
Reproductive/menstrual status reassessment*	Yes	At 6 months	Annually
Pregnancy test (active WOCBP only)	Mandatory negative (<50 mIU/mL)	Weekly x4, then monthly or fortnightly**	Monthly or fortnightly**, 4 weeks after stopping

WOCBP = women of childbearing potential (active menstrual cycles confirmed); LDH = lactate dehydrogenase; TSH = thyroid-stimulating hormone; HbF = fetal haemoglobin; eGFR = estimated glomerular filtration rate; ADL = activities of daily living.

** Reassess menstrual status and pubertal staging annually or if chelation regimen changes substantially, to identify any change in reproductive risk category.*

*** Monthly for women with regular cycles; every 2 weeks for women with irregular cycles; apply only to active WOCBP as stratified in Table 3.*

Thrombosis monitoring requires a baseline risk assessment documenting splenectomy status, prior VTE, platelet count, known thrombophilia, and immobility. At every visit, clinicians must specifically ask about limb swelling, leg pain, pleuritic chest pain, and shortness of breath. Any suspicion of VTE warrants immediate imaging and clinical assessment, with thalidomide withheld pending the result, consistent with the EMA SmPC.⁸

Component 4: Response Assessment and Treatment Continuation Criteria

Response should be formally assessed at six months. The definitions below are derived from the Thal-Thalido study data.³ An excellent response is a haemoglobin rise of 3 g/dL or more with transfusion independence. A good response is a haemoglobin rise of 2 g/dL or more with a meaningful reduction in transfusion frequency. A partial response is a haemoglobin rise of 1 g/dL or more with some reduction in transfusion burden. A haemoglobin rise of less than 1 g/dL with no meaningful reduction in transfusion frequency after six months at therapeutic dose constitutes treatment failure and should lead to discontinuation.

Dose should be reassessed at three months. If there is no HbF rise and no haemoglobin improvement after three months at the starting dose, and there is no Grade 2 or worse neuropathy, dose escalation to the upper end of the recommended TDT range may be considered before declaring treatment failure. Any dose escalation must be accompanied by neurological reassessment at four weeks.

Component 5: Pharmacovigilance Reporting to DRAP

DRAP was established under the DRAP Act 2012 and its pharmacovigilance remit covers all marketed and off-label drugs.¹⁰ Since November 2024, online Individual Case Safety Report (ICSR) e-Reporting through the DRAP portal has been mandatory for all registration holders.¹⁰ Centres prescribing thalidomide for TDT are expected to report serious adverse drug reactions through this system.

Events requiring immediate reporting within 24 hours: confirmed pregnancy or suspected fetal exposure in any patient on thalidomide; suspected Stevens-Johnson

syndrome or toxic epidermal necrolysis. Events requiring reporting within 15 calendar days: Grade 3 or 4 peripheral neuropathy; any confirmed VTE or arterial thrombotic event; Grade 4 neutropenia or febrile neutropenia; any serious unlisted adverse drug reaction.

Every centre should maintain a local register of all ICSR submissions alongside the patient registration database. The register should be reviewed at least annually by the centre's clinical governance lead. Any cluster of similar adverse events should trigger an immediate review of prescribing practice and notification to DRAP regardless of timelines.

Discussion

The central argument of this paper is that a safety framework for thalidomide in Pakistani TDT must be built around the patients who are actually being treated, not the patients who would be treated in a well-resourced European or North American setting. S.T.E.P.S. was designed in 1999 for a US population in which women of childbearing age who receive thalidomide are, by default, presumed to be potentially fertile.⁵ That presumption was reasonable for the ENL and later myeloma populations the programme was built for. It does not hold for a population of young Pakistani TDT patients in whom 82% have hypogonadism,¹¹ many will never menstruate, and some will not survive to adulthood without better transfusion and chelation. The teratogenic risk of thalidomide in this population is real but it applies to a subset, not the whole group. A framework that treats every female patient the same way fails to protect the ones who need protecting and burdens the ones who do not.

This does not diminish the severity of the teratogenic risk. A single fetal exposure to thalidomide causing phocomelia in a Pakistani child, born of a mother who was given the drug without any reproductive assessment, would be a preventable catastrophe. The risk is low in absolute terms in this population. It is not zero. The point of Table 3 is to find the patients for whom it is real, assess them properly, and apply intensive protection to them.

The evidence base for thalidomide in TDT is growing. The Thal-Thalido study³ and the 2026 meta-analysis⁶ show meaningful clinical benefit in a population with very

limited alternatives. Stem cell transplantation remains inaccessible for most Pakistani families. Gene therapy is not available in this setting. Luspatercept has shown efficacy in TDT but its cost and current access in Pakistan are prohibitive. Thalidomide, at 2 to 5 mg/kg/day, is cheap, available, and produces a response in the majority of treated patients. The argument for using it responsibly is not difficult to make.

What is needed now is for that responsible use to happen in practice. We call on DRAP to consider a national thalidomide registry for TDT, along the lines of the FDA REMS system and the EMA Risk Management Programme for Thalidomide BMS.⁸ We call on the Pakistan Society of Haematology and thalassaemia organisations to adopt this framework, or an equivalent, as a standard of care. And we call on individual prescribers, at every centre, to register their patients, assess reproductive risk properly, document monitoring, and report to DRAP when something goes wrong. Off-label prescribing does not reduce responsibility. It is the clinician's decision to prescribe, and it is the clinician's responsibility to monitor.

Conclusion

Thalidomide has real clinical benefit in a substantial proportion of Pakistani TDT patients who cannot access transplantation and have failed hydroxyurea. Its risks, particularly teratogenicity and peripheral neuropathy, are serious and well documented. In the Pakistani TDT population, however, those risks apply differently from Western populations. Most female patients are amenorrhoeic from iron-overload-driven hypogonadism. A framework that ignores this gives the appearance of safety without providing it.

The five-component framework proposed here tries to match the level of protection to the level of risk in each patient. It requires no special technology. It requires clinical assessment, accurate documentation, and the discipline to report adverse events. That is achievable at every centre prescribing this drug. What is not acceptable is the current situation, in which a known teratogen is being given to a poorly characterised population without registration, without reproductive risk assessment, and without any reporting pathway when harm occurs.

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