Current management of Thalassemia Syndromes in Thailand: past, present and future

Vip Viprakasit, M.D., D.Phil.(Oxon)
Department of Pediatrics and Thalassemia Center
Faculty of Medicine, Siriraj Hospital
Mahidol University, THAILAND
Why Thailand?
Thailand first reported “Thalassemia” in non-Mediterranean population

Figure 1 | An early clinical study of thalassaemia in Asia. These children have haemoglobin-E thalassaemia, which is particularly common in Thailand. The remarkable clinical heterogeneity of this condition was already obvious in 1954. Reproduced with permission from Ref. 77 © (1956) Elsevier Science.


Prof. Supa Na-Nakorn
Prof. Soodsakorn Tuchinda
Prof. Prawase Wasi
Prof. Pensri Pootrakul
Prof. Voravarn Tanphaichitr
Prevalence of thalassaemia and hemoglobinopathy in Asia Pacific Region

Epidemiology of thalassemia syndromes in Thailand

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Pregnancy at risk</th>
<th>New cases</th>
<th>Surviving cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>β thal major</td>
<td>2,500</td>
<td>625</td>
<td>6,250</td>
</tr>
<tr>
<td>Hb Bart’s hydrops</td>
<td>5,000</td>
<td>1,250</td>
<td>0</td>
</tr>
<tr>
<td>β thal/ Hb E</td>
<td>13,000</td>
<td>3,250</td>
<td>97,500</td>
</tr>
<tr>
<td>Hb H disease</td>
<td>28,000</td>
<td>7,000</td>
<td>420,000</td>
</tr>
<tr>
<td>Total</td>
<td>48,500</td>
<td>12,125</td>
<td>523,750</td>
</tr>
</tbody>
</table>

Source: thalassemia Foundation of Thailand 1998

Thalassemia is our major health burden and most important genetic disease in Thailand
Our Annual National Thalassemia Meeting since 1989

Thalassemias got talents!!
Thal R Thai project (start in Dec 2011)
Preliminary data on our national thalassemia registry (ThalRThai): Age distribution

Vip Viprakasit, unpublished data
### Preliminary data on our national thalassemia registry (ThalRThai): types of thalassemia

<table>
<thead>
<tr>
<th>Type of thalassemia syndromes</th>
<th>Total (n=1,768)</th>
<th>TDT (n=1,188)</th>
<th>NTDT (n=580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb H</td>
<td>156 (8.8%)</td>
<td>33 (2.8%)</td>
<td>123 (21.2%)</td>
</tr>
<tr>
<td>Hb Bart's Hydrops</td>
<td>9 (0.5%)</td>
<td>6 (0.5%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Hb H-CS</td>
<td>62 (3.5%)</td>
<td>19 (1.6%)</td>
<td>43 (7.4%)</td>
</tr>
<tr>
<td>(\beta)-thal major</td>
<td>201 (11.4%)</td>
<td>188 (15.8%)</td>
<td>13 (2.2%)</td>
</tr>
<tr>
<td>(\beta)-thal/Hb E</td>
<td>1098 (62.1%)</td>
<td>845 (71.1%)</td>
<td>253 (43.6%)</td>
</tr>
<tr>
<td>(\beta)-thal intermedia</td>
<td>9 (0.5%)</td>
<td>5 (0.4%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>143 (8.1%)</td>
<td>47 (4.0%)</td>
<td>96 (16.6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>90 (5.1%)</td>
<td>45 (3.8%)</td>
<td>45 (7.8%)</td>
</tr>
</tbody>
</table>

Vip Viprakasit, unpublished data
α- and β-thalassemias are the most common genetic disease found in Thailand

- Although, thalassemia syndromes were reported in Asian population for the first time from Siriraj Hospital since 1950s’

- There has been no data on their long term survival and causes of TM or TDT’s death from our current clinical management

- Moreover, there was no hitherto report on a long term survival of NTDT esp. Hb H and HbE/β thalassemia

Survival analysis in Thai thalassemia patients


Prof. Sudsakorn Tuchinda
Prof. Vinai Suvatte
Prof. Chularatana Mahasandana
Prof. Voravarn S. Tanphaichitr
Milestone years of Thailand National Health Registry Database in association with Siriraj’s Thalassaemia Registry

1st patient was born 1961

Start Siriraj hospital registry 1974

Start Thailand National Health Registry database

1996

At present study

2,570 patients could be identified

Data on causes of mortality available

4,303 patients were registered
Diagnosis of 4,303 thalassemia patients since 1970s’

<table>
<thead>
<tr>
<th>Total thalassaemia patients from hospital registry</th>
<th>β-thal/Hb E, n(%)</th>
<th>2,623 (61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=4,303 (since Jan 1974- Dec 2013)</td>
<td>β-thal major, n(%)</td>
<td>317 (7.3)</td>
</tr>
<tr>
<td></td>
<td>Hb H, n(%)</td>
<td>691 (16)</td>
</tr>
<tr>
<td></td>
<td>Hb H/Hb CS, n(%)</td>
<td>672 (15.7)</td>
</tr>
</tbody>
</table>

Can be verified using the national registry?

No

N=1,733

| β-thal/Hb E, n(%) | 1,018 (59) |
| β-thal major, n(%) | 152 (8.8) |
| Hb H, n(%)     | 305 (17.4) |
| Hb H/Hb CS, n(%) | 258 (14.8) |

N=2,570

| β-thal/Hb E, n(%) | 1,605 (62) |
| β-thal major, n(%) | 165 (6.4) |
| Hb H, n(%)     | 386 (15.5) |
| Hb H/Hb CS, n(%) | 414 (16.1) |

Alive in 2013?

No

N=189

Yes

N=2,381

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017

Kaplan-Meier survival curves for all types of thalassaemia syndromes in Thailand (n = 2,570)

Cumulative survival probability

Age (years)

β-thalassaemia/HbE
HbH
HbH/HbCS
HbE/β thalassaemia
β-TM
β-TMC

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017

Kaplan-Meier survival curves by decade of birth cohort

Overall survival of β thalassemia syndrome seems to get improved in the last two decades

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017
Mortality rates (/100,000) in β- but not α-thalassemia syndromes are higher than general age-sex matched population of Thailand

<table>
<thead>
<tr>
<th>Mortality rate/100,000</th>
<th>All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta\text{ thal/Hb E})</td>
<td>681.3155564</td>
</tr>
<tr>
<td>Age-matched Thai general population controls</td>
<td>216.1643617</td>
</tr>
<tr>
<td>Death rate ratio ((\beta\text{ thal/Hb E / general population}))</td>
<td>3.151840346</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
</tr>
<tr>
<td>(\beta\text{ thal major})</td>
<td>1286.48838</td>
</tr>
<tr>
<td>Age-matched Thai general population controls</td>
<td>170.3499178</td>
</tr>
<tr>
<td>Death rate ratio ((\beta\text{ thal major / general population}))</td>
<td>7.552034049</td>
</tr>
<tr>
<td>p-value</td>
<td>0.024</td>
</tr>
<tr>
<td>(\text{Hb H disease})</td>
<td>137.6179656</td>
</tr>
<tr>
<td>Age-matched Thai general population controls</td>
<td>209.896104</td>
</tr>
<tr>
<td>Death rate ratio ((\text{Hb H /general population}))</td>
<td>0.655648023</td>
</tr>
<tr>
<td>p-value</td>
<td>0.541</td>
</tr>
<tr>
<td>(\text{Hb H/Hb CS})</td>
<td>130.7394883</td>
</tr>
<tr>
<td>Age-matched Thai general population controls</td>
<td>181.2149886</td>
</tr>
<tr>
<td>Death rate ratio ((\text{Hb H/Hb CS /general population}))</td>
<td>0.721460677</td>
</tr>
<tr>
<td>p-value</td>
<td>0.505</td>
</tr>
</tbody>
</table>

*p<0.05
NS
Causes of death (%) in β thal major (TM) compared to the general age-sex matched Thai population controls

This data indicates that our βTM patients have received suboptimal blood transfusion country-wide

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017
Causes of death (%) in β thal/Hb E compared to the general age-sex matched Thai population controls

This data indicates that our β thal/Hb E patients who have both TDT and NTDT phenotypes might not been properly treated country-wide.

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017
Standard of care determine survival in Thai β thal/Hb E thalassemia patients

Kaplan-Meier survival curves for HbE/β-thalassaemia patients who were treated at Siriraj Thalassaemia Centre (n = 557) compared with other hospitals (n = 1,048)

- Most thalassaemia patients remain suffer from several disease-related clinical complications
- Optimal management for the clinical consequences can improve their long-term survival

Jansutjawan S. & Viprakasit V. Manuscript in preparation 2017
How can we achieve the best care for thalassemia patients?
1st Thalassemia Center to receive SITA (Sultan Bin Khalifa International Thalassemia Award) in 2014
Thalassemia Care 2017: First step is adequate blood transfusion
Early and Adequate Blood Transfusion Can Improve Life Quickly in Young TDT Patients
What will you get when you transfuse your TDT patients adequately?

Toddler period
What will you get when you transfuse your TDT patients adequately?

Early childhood period
What will you get when you transfuse your TDT patients adequately?

Teenager period
I am treating a little “Iron Man”
How can I do the best for him?

How can we make ICT to be more effective for him?
- Clinical sciences
- Socioeconomic
How can we maximize our thalassemia management

- Better iron monitoring
- Availability of iron chelators
- Continuous medical education
- Future clinical studies
How can we maximize our thalassemia management

- Better iron monitoring
- Availability of iron chelators
- Continuous medical education
- Future clinical studies
Thailand’s software for liver & cardiac T2* evaluation

Pairash Saiviroonporn, PhD
Mahidol University

John Wood, MD, PhD
CHLA

USA: CHLA & CHI
Stephan G. Erberich, PhD
Bangkok (Siriraj Hospital)
Dr. Rungroj Krittayaphong, MD
Siriraj grant for research development (R015233005): Mar 2009 – Oct 2010

N = 90

PI: Rungroj Krittayaphong Vip Viprakasit

Reference Site

Siriraj

Scan

t<10 days (n=37)

Black blood

Black blood

White blood

ROI-based

ROI-based

Pixel-wise

Exp (Truncation)

Exp

Exp+Const

He et al. JMRI 2007;25(6):1205-9

Westwood et al. JMRI 2003;18:33-9

CMR Tools (London, UK)

CHLA's (USA) and Siriraj's software

Siriraj grant for research development (R015233005): Mar 2009 – Oct 2010

N = 90

PI: Rungroj Krittayaphong Vip Viprakasit

Reference Site

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Scan

t<10 days (n=37)

Black blood

Black blood

White blood

ROI-based

ROI-based

Pixel-wise

Exp (Truncation)

Exp

Exp+Const

He et al. JMRI 2007;25(6):1205-9

Westwood et al. JMRI 2003;18:33-9

CMR Tools (London, UK)

CHLA's (USA) and Siriraj's software
Black Blood Images and T2* maps

Normal

Marginal

Mild

Severe

\[ \text{TE}_1 \quad \text{TE}_4 \quad \text{TE}_8 \quad \text{T2* map} \quad \text{msec} \]

Saiviroonporn P & Viprakasit V. et al. JCAI 2011
mg/g dry weight

LIC = 2.5 (normal [< 3])

4.3 (mild [3-7])

8.7 (moderate [7-15])

22.7 (severe [> 15])
Improved R2* liver iron concentration assessment using a novel fuzzy c-mean clustering scheme

Parash Saiviroonpon1*, Vip Viprakast2 and Rungruj Krittayaphong3

Abstract
Background: In thalassemia assessing iron overload is of importance. A common tool for assessing relative iron overload range due to its C-Mean (FCM) clustering the parenchyma. Our study further assessed p-scheme for routine clinic.

Methods: Segmentation studies from 147 thalassaemia cases were performed on the a to execute the MIX-FCM m and was compared to T (InQ) to its median to e.

Results: 2D-FCM cluster for other ranges (where methods allows MIX-FCM with 10.3 ± 9.0% and 7.0 OP-MIX-FCM result, with

Conclusion: Our propose method benefits from the segmentation accuracy c scheme (OP-MIX-FCM). F the severe iron overload.

Keywords: FCM, Liver iron overload, Liver T2* measurement, Liver segmentation, Thalassemia
How can we make this MRI facility available to all centers in Thailand?

**Asia-Pacific network on Iron overload Assessment by MRI: APIA-MRI**

- **Center site (CHLA)**
- **Regional center site (Sriraj)**
  - Sub-country center site
    - Local site
    - Local site
  - Local site
- **Country center site**
  - Local site
  - Local site

Phase II-III: Validated in Asia countries start from Jan 2012 –
APIA Sites in Thailand (including Siriraj)

Thailand
- 3 Clinical Sites
- 3 Investigative Sites
- 4 Research Sites

The Philippines
- 2 Investigative Sites

Brunei
- 1 Investigative Sites
Serum ferritin in the diagnosis of cardiac and liver iron overload in thalassaemia patients real-world practice: a multicentre study

<table>
<thead>
<tr>
<th>Variables</th>
<th>number (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td>18.8 ± 12.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>189 (46.7)</td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>216 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Height (centimeter)</td>
<td></td>
<td>149.6 ± 14.8</td>
</tr>
<tr>
<td>Weight (kilogram)</td>
<td></td>
<td>42.6 ± 12.9</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- β-thalassemia major</td>
<td>35 (8.6)</td>
<td></td>
</tr>
<tr>
<td>- β – thalassemiaHbE</td>
<td>296 (73.1)</td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td>74 (18.3)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (year)</td>
<td></td>
<td>5.4 ± 11.7</td>
</tr>
<tr>
<td>Age at 1st transfusion (year)</td>
<td></td>
<td>3.9 ± 5.3</td>
</tr>
<tr>
<td>Type of blood transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>48 (11.9)</td>
<td></td>
</tr>
<tr>
<td>- Occasional</td>
<td>61 (15.1)</td>
<td></td>
</tr>
<tr>
<td>- Regular</td>
<td>296 (73.1)</td>
<td></td>
</tr>
<tr>
<td>Total transfusion in 1 year (milliliter)</td>
<td>156.0 ± 78.0</td>
<td></td>
</tr>
<tr>
<td>Average pre-transfusion Hb level (gram%)</td>
<td>8.5 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td></td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>History of cardiac dysfunction</td>
<td></td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>History of elevated ALT more than twice upper limit</td>
<td>38 (9.4)</td>
<td></td>
</tr>
<tr>
<td>History of splenectomy</td>
<td></td>
<td>80 (19.8)</td>
</tr>
</tbody>
</table>

- A total of 405 patients were included
- A mean age of 18.8 ± 12.5 years and 46.7% were males,
- 296 (73.1%) were TDT, 61 (15.1%) were NTDT and 48 (11.9%) were non-transfused.
- Mean serum ferritin level was 2318.4 ± 2376.0 ng/ml.
Prevalence and Predictors of Cardiac and Liver Iron Overload in Patients with Thalassemia: A Multicenter Study Based on Real-World Data

Runroj Krittayaphong, Vip Viprakasit, Pairash Saiviroonporn, Noppadol Siritanaratkul, Suviporn Siripornpitak, Arunotai Meekaewkunchorn, Thawatchai Kirawittaya, Pornpun Sripornsawan, Arunee Jetsrisuparp, Jiraporn Srinakarin, Peerapon Wong, Nuttaporn Tira Phalakornkul, Phakatip Sinlapamongkolkul, John Wood
Improving profile of cardiac iron overload in Thailand after T2*-MRI-Siriraj hospital

N=252

T2*<20 ms
25% → 2%

Viprakasit V. unpublished data 2017
Improving profile of liver iron overload in Thailand after T2*-MRI – Siriraj hospital

Viprakasit V. unpublished data 2017
How can we maximize our thalassemia management

- Better iron monitoring
- **Availability of iron chelators**
- Continuous medical education
- Future clinical studies
Pharmacological and Biochemical properties of current and under-investigated iron chelators for iron overload

<table>
<thead>
<tr>
<th>Deferoxamine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoichiometry of iron binding</td>
<td>Hexadentate (1:1)</td>
</tr>
<tr>
<td>Molecular weight (Da)</td>
<td>559</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>30 min</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>6 h</td>
</tr>
<tr>
<td>Route of iron elimination</td>
<td>Urinary and fecal</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous or intravenous</td>
</tr>
<tr>
<td>Recommended dose</td>
<td>25 – 60 mg/kg/day over 8 – 24 h</td>
</tr>
</tbody>
</table>

Deferiprone (GPO-L-ONE®) monotherapy reduces iron overload in transfusion-dependent thalassemias: 1-year results from a multicenter prospective, single arm, open label, dose escalating phase III pediatric study (GPO-L-ONE; A001) from Thailand

Vip Viprakasit,1,* Issarang Nuchprayoon,2 Ampaiwan Chuanumrit,3 Kitti Torchuras,4 Bunchoo Pontanakul,1 Jiraporn Laohamatas,5 Somdet Srichairatanakool,6 Julaporn Poolam,7 Siriwat Supajaksem,8 Prapat Suryaphol,8 Voravarn S. Tanphachitr,1,9 and Sooodsorn Tuchinda9

Accessibility to iron chelators including deferoxamine and deferasirox remains obscure in many developing countries. To provide an alternative, the government pharmaceutical organization of Thailand (GPO) manufactured deferiprone, which has similar bioequivalence to the standard iron chelator deferoxamine, for patients with severe β thalassemia, age range 3.2-19 years, were recruited to a 1-year multicenter prospective, single arm, open label, dose escalating Phase III study of deferiprone to determine its clinical efficacy and safety. Sixty-four patients (87.6%) completed the study with good compliance (94%). Average deferiprone dose was 79.1-4.3 mg/kg/day. Overall, mean serum ferritin (SF) levels at 1 year were not significantly changed from baseline. However, 45% of patients (response group) had SF reduced >15% from baseline at 1 year with a median reduction of 1.065 ng ml-1. Baseline SF was the major factor that predicts clinical efficacy; patients with baseline SF >3,500 ng ml-1 had the most significant fall of SF at 1 year. A subgroup analysis by MRI-T2* confirmed that the response group had higher baseline liver iron and deferiprone could significantly reduce liver iron overload and normalize levels of ALT at 1 year. Although, gastrointestinal irritation (20.5%) was the most common drug-related adverse events (AEs) followed by transaminits (16.4%) and neutropenia (6.6%), all patients were well tolerated. There was no mortality and agranulocytosis found in this trial. Monotherapy of deferiprone with appropriate dose adjustment and monitoring for adverse events appeared to be an effective chelation therapy in some patients with good compliance and acceptable safety profiles. Am. J. Hematol. 88:251–260, 2013.

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Introduction

Even though, at present, stem cell transplantation offers a curative measure for severe thalassemia syndrome with transfusion dependency (Thalassemia Major; TM), this approach is limited due to possible late effects [1], donor availability, health resources, and expertise [2]. Splenectomy can be used only in limiting number of patients with hypersplenism and could not ameliorate classic phenotypic in most severe patients. Therefore patients with severe thalassemia syndrome still rely on regular blood transfusion to improve both quality of life [3] and long-term survival [4]. As a direct result, transfusional iron overload is unavoidable and this could cause fatal complications including cardiac siderosis and failure, endocrinopathies, delay puberty, liver fibrosis and failure, and increased susceptibility to infectious diseases [5–7]. Problems related to iron overload seem to be underestimated especially in the Asia Pacific region where there is the highest prevalence of the globin disorders in the world [8]. A recent study has shown that the average levels of serum ferritin (SF), the widely used surrogate marker for tissue iron store and iron overload, was highest in this region compared to Europe or the Middle East [9]. Several factors contributing to this higher iron burden in Asia Pacific including a limited patients’ access to the standard iron chelator; desferoxamine (DFO) due to its cost and availability. Moreover, administration of DFO by continuous subcutaneous infusion is painful and highly cumbersome causing a rather low compliance in many patients and therefore uncertain efficacy in reducing iron overload especially in pediatric population. In a cross sectional study of Thai pediatric patients with severe β-thalassemia syndromes, it was shown that the majority of patients (86%) had a poor compliance with deferoxamine

Development of generic deferiprone in Thailand (GPO-L-ONE)

> 10,000 thalassemia patients received GPO-L-ONE in Thailand since 2012

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Deferasirox: an oral iron chelator

N-substituted bis-hydroxyphenyl-triazoles

• Deferasirox has been available since 2006 in Thailand
• All major clinical trials have been conducted in Thailand; EPIC, EPIC-Cardiac substudy, CORDELIA, HYPERION, THALASSA, NESO, THETIS
• New formulation studies: ECLIPSE CALYPSO, JUPITER
• Through our local EXPAP program 
  \[(1 + 3) > 1500\] patients are receiving deferasirox in Thailand
- How can we maximize our thalassemia management
  - Better iron monitoring
  - Availability of iron chelators
  - **Continuous medical education**
  - Future clinical studies
1st Pan Asian Conference on Thalassemia & Haemoglobinopathies: Feb 2012
Exchanging expertise in iron science and research

The 3rd Asia Pacific Iron Academy Conference
3–4 November 2012
The Grand Hotel, Taipei, Taiwan
How can we maximize our thalassemia management

- Better iron monitoring
- Availability of iron chelators
- Continuous medical education
- Future clinical studies
Therapeutic actions for $\gamma$-globin gene induction in the $\beta$-thalassemias

Hematologic responses to fetal globin gene inducers in $\beta$-thalassemia patients

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Mechanism of Action</th>
<th>Thalassemia Syndromes</th>
<th>Increase in Total Hb (g/dL)</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Azacytidine</td>
<td>Hypomethylation</td>
<td>TI</td>
<td>2.5 [1.5–4]</td>
<td>5/5 +/- cytotoxicity</td>
</tr>
<tr>
<td>Sodium phenylbutyrate (SPB)</td>
<td>HDACi effect</td>
<td>TI and TM</td>
<td>2.1 [1.2–2.8]</td>
<td>4/8 untransfused</td>
</tr>
<tr>
<td>Hydroxyurea (HU)</td>
<td>Cytotoxicity and erythroid</td>
<td>Hb E/$\beta$ thal</td>
<td>2.0 [1-3.3]</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>regeneration</td>
<td></td>
<td>2.7 [2.2-3.2]</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.6 [0-1.7]</td>
<td>11/13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
<td>7/19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
<td>3/8</td>
</tr>
</tbody>
</table>

TI = $\beta$-thalassemia intermedia; TM = $\beta$-thalassemia major

Perrine, S. P. Hematology 2005;2005:38-44
No trials comparing hydroxyurea with placebo or standard care were found.

The effect of hydroxyurea on transfusion frequency was not reported.

The overall quality for the outcomes reported was graded as very low.
CLINICAL EFFICACY OF HYDROXYUREA (HU) IN CHILDREN AND ADOLESCENTS WITH BETA-THALASSEMIA SYNDROMES

Surakarn Jansutjawan, Vip Viprakasit

Division of Hematology and Oncology, Department of Pediatrics and Siriraj-Thalassemia Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

A retrospective cohort of our registry

- **β-thalassemia treated with HU (n=28)**
  - Excluded patients: Poor compliance (n=1), Receive HU < 3 months (n=1)
  - **Included patients (n=26)**
    - **β-thal major (n=3)**
      - No clinical response to HU
    - **β-thal intermedia (n=3)**
      - Clinical response to HU
    - **β-thal/HbE (n=20)**
      - TD-β/HbE (n=4)
        - No clinical response to HU
      - **NTD-β/HbE (n=16)**
        - Good-responder (n=6; 37.5%)
        - Partial-responder (n=6; 37.5%)
        - Non-responder (n=4; 25%)

No clinical response to HU
Partial response to HU in Thai β-thal intermedia (NTDT)

Figure 1. CT skull in patient No.5 (Pre- and Post-treatment (1 yr) with HU; A and B)
Clinical response to Thai pediatric patients with NTD-β/HbE

- β-thal/HbE (n=20)
  - TD-β/HbE (n=4)
    - No clinical response to HU
  - NTD-β/HbE (n=16)
    - Good-responder (n=6; 37.5%)
      - Increased Total Hb > 1 g/dL
    - Partial-responder (n=6; 37.5%)
      - Increased Total Hb 0.05-1 g/dL and Absolute HbF > 0.5 g/dL
    - Non-responder (n=4; 25%)
      - No Change in Total Hb and Absolute HbF

75% of NTD-Hb E/β thal responded to HU

Graph showing total Hb F increment (g/dL) over time for different patients and responses to HU.
Demographic data and baseline laboratory test analysis in 3 subgroups of NTD-β/HbE

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Good-responder (n=6)</th>
<th>Partial-responder (n=6)</th>
<th>Non-responder (n=4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Female</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0.302</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>134.5 (101, 321)</td>
<td>189.5 (61, 286)</td>
<td>264.5 (155, 303)</td>
<td>0.264</td>
</tr>
<tr>
<td>Age of diagnosis (months)</td>
<td>24.0 (0, 84)</td>
<td>45.0 (12, 106)</td>
<td>31 (20, 148)</td>
<td>0.607</td>
</tr>
<tr>
<td>Age at start of HU treatment (months)</td>
<td>100.0 (81, 204)</td>
<td>131.0 (43, 246)</td>
<td>200.0 (81, 260)</td>
<td>0.464</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.2 (17.3, 48.4)</td>
<td>26.2 (13.9, 55.6)</td>
<td>43.7 (24.2, 52.1)</td>
<td>0.264</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>126.0 (114, 149)</td>
<td>131.0 (96, 158)</td>
<td>156.0 (122, 167)</td>
<td>0.229</td>
</tr>
</tbody>
</table>

Baseline laboratory test (average 6 months before HU treatment)

<table>
<thead>
<tr>
<th></th>
<th>Good-responder (n=6)</th>
<th>Partial-responder (n=6)</th>
<th>Non-responder (n=4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hb (g/dL)</td>
<td>6.7 (6.0, 7.3)</td>
<td>6.7 (6.5, 7.6)</td>
<td>6.6 (5.8, 7.4)</td>
<td>0.739</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>21.6 (20.5, 23.7)</td>
<td>23.0 (21.7, 24.8)</td>
<td>21.6 (20.7, 23.8)</td>
<td>0.287</td>
</tr>
<tr>
<td>Hb F (%)</td>
<td>40.9 (37.7, 45.4)</td>
<td>46.2 (10.9, 61.3)</td>
<td>17.8 (8.1, 28.8)</td>
<td>0.028</td>
</tr>
<tr>
<td>Absolute Hb F (g/dL)</td>
<td>3.2 (2.5, 3.7)</td>
<td>3.1 (0.7, 4.9)</td>
<td>1.0 (0.5, 1.5)</td>
<td>0.038</td>
</tr>
<tr>
<td>WBC count (x10³/ul)</td>
<td>10.6 (7.2, 13.2)</td>
<td>10.1 (6.5, 14.7)</td>
<td>13.4 (10.0, 17.0)</td>
<td>0.191</td>
</tr>
<tr>
<td>Platelet count (x10³/ul)</td>
<td>297.5 (215, 903)</td>
<td>577.5 (341, 828)</td>
<td>745.5 (414, 983)</td>
<td>0.068</td>
</tr>
<tr>
<td>RBC count (x10⁶/ul)</td>
<td>3.9 (2.7, 4.4)</td>
<td>3.8 (3.2, 4.2)</td>
<td>3.5 (3.0, 4.4)</td>
<td>0.934</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>57.7 (51.1, 77.8)</td>
<td>59.7 (55.4, 71.8)</td>
<td>62.2 (53.9, 70.0)</td>
<td>0.826</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>18.2 (15.7, 22.4)</td>
<td>18.8 (15.9, 20.3)</td>
<td>18.3 (16.8, 20.9)</td>
<td>0.976</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>30.5 (28.7, 32.7)</td>
<td>29.8 (28.4, 32.2)</td>
<td>30.6 (26.2, 33.2)</td>
<td>0.779</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>28.5 (22.5, 33.0)</td>
<td>30.2 (24.2, 34.0)</td>
<td>30.2 (25.6, 32.6)</td>
<td>0.948</td>
</tr>
<tr>
<td>NRC (/100WBC)</td>
<td>8.0 (5, 477)</td>
<td>41.5 (16, 1059)</td>
<td>244.0 (0, 2515)</td>
<td>0.293</td>
</tr>
<tr>
<td>ANC (x10³/ul)</td>
<td>5.4 (3.8, 7.4)</td>
<td>5.2 (2.3, 7.4)</td>
<td>5.8 (4.4, 9.6)</td>
<td>0.760</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>3.5 (2.9, 4.5)</td>
<td>6.3 (3.2, 8.0)</td>
<td>6.8 (2.0, 14.1)</td>
<td>0.229</td>
</tr>
</tbody>
</table>
Determination of genetic modifiers associated with HU response in Thai NTD-β/HbE

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP number</th>
<th>Chromosome</th>
<th>Allele</th>
<th>Minor Allele</th>
<th>Minor Allele Frequency</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6γ-Globin Promoter (XmnI)</td>
<td>rs7462144</td>
<td>11p15</td>
<td>C/T (-/+)</td>
<td>T (+)</td>
<td>0.45</td>
<td>14.3 (0.7,277.7)</td>
<td>0.029</td>
</tr>
<tr>
<td>HBBP1</td>
<td>rs2071348</td>
<td>11p15</td>
<td>A/C</td>
<td>C</td>
<td>0.45</td>
<td>14.3 (0.7,277.7)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>rs1427407</td>
<td>2p16</td>
<td>G/T</td>
<td>T</td>
<td>0.27</td>
<td>6.7 (0.3,133.6)</td>
<td>0.155</td>
</tr>
<tr>
<td>BCL11A</td>
<td>rs766432</td>
<td>2p16</td>
<td>A/C</td>
<td>C</td>
<td>0.32</td>
<td>8.2 (0.4,162.3)</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>rs11886868</td>
<td>2p16</td>
<td>C/T</td>
<td>T</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>rs10189857</td>
<td>2p16</td>
<td>G/A</td>
<td>A</td>
<td>0.27</td>
<td>6.7 (0.3,133.6)</td>
<td>0.155</td>
</tr>
<tr>
<td>HBS1L-MYB</td>
<td>rs9376092</td>
<td>6q23</td>
<td>C/A</td>
<td>A</td>
<td>0.09</td>
<td>0.7 (0.1,9.0)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>rs9399137</td>
<td>6q23</td>
<td>T/C</td>
<td>C</td>
<td>0.09</td>
<td>0.7 (0.1,9.0)</td>
<td>1</td>
</tr>
</tbody>
</table>

All of non-responder had **XmnI**; -/-

At present in my clinic, we perform **XmnI** genotype before the use of HU

Jensatjawan S & Viprakasit V, 2017
A phase 1 dose-escalation study: safety, tolerability, and pharmacokinetics of FBS0701, a novel oral iron chelator for the treatment of transfusional iron overload


- Tridentate chelator
- Binds Fe(III) with very high affinity
- Preclinical toxicological studies
  - Higher no-observable-adverse-effect level (NOAEL) compared to deferasirox
  - Suggesting favorable clinical safety profile
A phase 2 study of the safety, tolerability and pharmacodynamics of FBS0701, a novel oral iron chelator, in transfusional iron overload

<table>
<thead>
<tr>
<th></th>
<th>14.5 mg/kg/day</th>
<th>29 mg/kg/day</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean net change in hepatic iron (mg/g-dw)</td>
<td>3.1</td>
<td>–0.3</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>% with net iron reduction</td>
<td>29</td>
<td>44</td>
<td>NS</td>
</tr>
</tbody>
</table>

Associated with renal cell carcinoma in mouse model: STOP STUDY
SP-420: a new generation oral iron chelator (Sideris)

- SP-420 development is based on deferitrin
  - orally available
  - modified to reduce toxicity
- More effective iron chelator than existing (in animal trials)
  - better chelating efficiency
  - improved bioavailability
  - higher tissue levels, esp. cardiac and pancreatic
  - reduced renal toxicity
- Improved formulation

Causing high incidence of renal toxicity: STOP STUDY
Novel Therapeutic Targets in Thalassemia

* Those studies are currently underway in Thailand
Being a thalassemia doctor is the best job in the medical world
Thailand is still at the forefront of Thalassemia management
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Pairash Saiviroonporn
Thidarat Suksangpleang
Suchada Ruengleung
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