1st Pan-Middle East Conference on Haemoglobinopathies

1–2 May 2009
Damascus, Syria

Conference Report

Dr Androulla Eleftheriou
Kaisa Immonen-Charalambous
# Contents

Dedication ................................................................................................................................. 3
Introduction ................................................................................................................................. 4
About the Organiser .................................................................................................................. 6
Conference Committees and Faculty ....................................................................................... 7
Haemoglobin disorders in the Eastern Mediterranean Region .............................................. 9
Scientific Programme ............................................................................................................... 14
Patients and Parents’ Programme ............................................................................................ 21
Status of Patient Care in Participating Countries ................................................................. 23
  Part 1: Medical Professionals ................................................................................................. 23
Status of Patient Care in Participating Countries ................................................................. 25
  Part 2: Patients’ Perspective .................................................................................................... 25
Conclusions and recommendations ......................................................................................... 31
Annex 1: Conference programme ......................................................................................... 34
Annex 2: Conference evaluation ............................................................................................ 37
Annex 3: Abstracts of presentations ........................................................................................ 38
Annex 4: EHA CME Accreditation ......................................................................................... 83
Dedication

This Conference Report is dedicated to the First Lady of the Syrian Arab Republic, Her Excellency Mrs Asma Al Assad, who kindly agreed to place the Conference under her patronage.

This kind gesture has given the Conference the attention and political weight it deserved, not only through the local media in Syria, but also throughout the Middle East region. We were extremely honoured that she was able to allocate some time from her busy schedule to meet us and discuss the status of haemoglobinopathies in Syria and the Middle East Region.

Mrs Al Assad’s charitable work is well known, not only locally and regionally, but worldwide. We are confident that her support will raise awareness of the cause of thalassaemia and sickle cell disease in Syria, the Middle East and across the world, helping to alleviate suffering and improve the lives of patients and their families.

The Board of the Thalassaemia International Federation recently decided to establish a “Global Circle of Dignitaries” from all over the world, to help promote efforts at national and regional levels. We are very proud to have Her Excellency Mrs Asma Al Assad as the first member of this Circle. We thank her most warmly, and hope many others will follow her example.

Panos Englezos
Co-Chair of the Organising Committee
President, Thalassaemia International Federation

Kusai Alzir, MD
Co-Chair of the Organising Committee
President, Patient's Friends Association
And Hereditary Blood Diseases, Syria
Introduction

The First Pan-Middle East Conference on Haemoglobinopathies gathered over 400 participants from 17 countries to Damascus, Syria on 1–2 May 2009. The conference was organised by the Thalassaemia International Federation in collaboration with the Syrian patients association “Thalassaemia Patients and Hereditary Blood Diseases”, under the auspices of the WHO Eastern Mediterranean Regional Office (EMRO) and the patronage of the First Lady of Syria, Her Excellency Mrs Asmaa Al-Assad.

This was the second regional event organised by the Federation, reflecting the accumulated experience of many years organising educational events at national and international levels. The new regional conferences focus on the specific needs of each region of the world, as well as the particular challenges faced by each country within the region. The first such event was the Pan-European Workshop on Thalassaemia held in Lisbon, Portugal in 2007. We have recognised that, although many healthcare challenges are specific to individual countries due to the great variety of health systems and difference in the quality of health services, nevertheless many regions of the world with similar cultural, religious and linguistic features share certain problems in the management and prevention of haemoglobin (Hb) disorders.

In the Eastern Mediterranean Region, haemoglobin disorders and their importance have long been under-recognised by governments because of a lack of reliable epidemiological information on the frequency of the diseases and their real medical, economic and psycho-social impact. Other factors contributing to this relative neglect include weak health infrastructures, other overriding health priorities, poor health literacy of the populations, and of course a lack of resources.

It was therefore the objective of the 1st Pan-Middle East Conference to raise the profile of haemoglobin disorders and gather relevant information for the region and for each country individually, in order to identify the causes for the lack of effective control programmes, but also to identify specific ways and areas where the Thalassaemia International Federation can provide support and achieve a measurable impact.

The Conference ran over two days and was divided into a scientific programme and a patients’ and parents’ programme. The scientific programme covered in depth the current state of art in the prevention and clinical management of haemoglobin disorders, as well as the latest research data on gene therapy and other innovative therapies. The faculty was comprised of internationally recognised authorities in each field (see list of faculty on p.7 and programmes in Annex 2). The European Haematology Association (EHA) accredited the conference with 12 CME units (Annex 3). Similarly, the patients/parents’ programme (Annex 2) extensively covered clinical management and other vital aspects from the patients’ perspective.

The conference attracted a total of 411 participants, with 237 health specialists, 140 patients and 15 parents from 15 countries. In order to facilitate the participation of delegates with limited financial resources, TIF operates a travel bursary programme for patients, parents and selected health professionals, with the criteria for the latter relating to their level of involvement in the treatment or prevention of Hb disorders in their country.
Translation
Translation facilities from Arabic to English and English to Arabic were provided for the patients programme only.

Educational material
A total of 800 copies of TIF’s educational books were distributed in the course of the conference to patients and health professionals:

- 300 *Guidelines for the Clinical Management of Thalassaemia, 2nd edition revised (2008)* in English
- 200 *About Thalassaemia* in Arabic
- 200 educational booklet sets in Arabic ("About β-thalassaemia", “About α-thalassaemia”, “About sickle cell disorders”)
- 50 *Patients’ Rights* in Arabic
- 50 *Guide to Establishing a Non-Profit Patient Support Organisation* in Arabic

Evaluation and information questionnaires
Four types of questionnaires were prepared for the conference. Three questionnaires were distributed to health professionals – one for obtaining information on the status of control programmes in their country, a second one for collecting detailed information on treatment in their country, and a third one for evaluation of the conference.

Patients and parents were asked to fill in a special patients’ information questionnaire. This was translated into Arabic and the responses obtained translated into English by an Arabic-speaking expert patient and TIF board member. The analysis of the questionnaires is found on page 28.

Recognition by WHO and at national levels
Official recognition was also confirmed through the patronage granted to the conference by the First Lady of the Syrian Arab Republic, Her Excellency Mrs Asma Al-Assad, who also invited the organisers to the Presidential Palace to discuss the topic. The official involvement of the WHO Eastern Mediterranean Regional Office (EMRO), represented by Regional Director Professor Hussein A Gezairy, underlined the importance given to haemoglobin disorders in the region and the recognition by WHO of the need to develop effective national control strategies in every Eastern Mediterranean country.

The conference opening ceremony gained the necessary political weight from the presence and contribution of the Syrian Ministry of Health, Dr Rida Said, and the Minister of Higher Education, Dr Ghiath Barakat, both of whom recognised the public health burden of haemoglobin disorders in Syria and the region as a whole and expressed their commitment on behalf of the government for progress on the national control programme.
About the Organiser

The Thalassaemia International Federation (TIF) is the global non-profit non-governmental organisation supporting the rights of patients with haemoglobin disorders across the world to better health and quality of life. Its membership comprises 94 member associations from 50 countries of the world. TIF’s mission is to promote equal access to optimal treatment for all patients through the establishment of effective control programmes.

One major role of TIF is to act as the united voice of patients with thalassaemia worldwide, and in this context it supports and assists existing patients/parents’ support associations and encourages the establishment of new ones.

One of the main challenges for TIF is to “bridge the gap” that exists between industrialised and developing countries – to extend the knowledge, experience and expertise gained in those countries where effective control programmes were first developed, to other affected countries across the world. TIF works closely with WHO headquarters and regional offices, European Union institutions, medical and research communities around the world, other disease-oriented associations, industry, and other relevant health-associated stakeholders towards achieving its mission for equal access of all patients to quality health care.

The International Thalassaemia Day is celebrated every year on the 8th of May and involves awareness-raising and educational activities as well as blood donation campaigns organised by national associations in their own countries across the world, around a specific theme publicised by the Thalassaemia International Federation.

TIF’s most important and successful tool for furthering its mission is its educational programme, which includes an extensive range of educational material and the organisation of local, national and international workshops and conferences focused on the needs of both patients/parents and health professionals. To date, TIF has organised over 50 local/national and 20 international workshops, as well as 13 international conferences, with the participation of over 18,000 health professionals and patients/parents from all over the world. TIF’s educational publications have been translated into up to 20 languages. These are available online at www.thalassaemia.org.cy. Printed copies can be ordered from its offices in Nicosia, Cyprus.
Conference Committees and Faculty

Three committees were formed – the Organising Committee, the Scientific Committee and the Advisory Committee. The Organising Committee was led by Dr Kusai Al Zir on behalf of the Syrian thalassaemia association “Thalassaemia Patients Friends Association And Hereditary Blood Diseases”, and Mr Panos Englezos, President of the Thalassaemia International Federation.

The Scientific Committee was chaired by Professor Ali Taher, Head of Haematology at American University of Beirut Medical Centre. The Advisory Committee included regional and international experts from a wide range of specialties. The patients/parents’ programme was led by board members of TIF from the region.

The faculty comprised 23 regional and international medical specialists. A number of patients and parents were also involved and actively participated in the development of the programmes and in the materialisation of the Conference.

---

### Scientific Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ali Taher, MD</strong></td>
<td>(President) Professor of Internal Medicine, Head of Haematology, American University of Beirut Medical Centre, Lebanon</td>
</tr>
<tr>
<td><strong>Amal El-Beshlawy, MD</strong></td>
<td>(Vice-President) Professor of Paediatric Haematology, Cairo University Hospital. President, Egyptian Thalassemia Association</td>
</tr>
<tr>
<td><strong>Maria-Domenica Cappellini, MD</strong></td>
<td>(Co-President) Professor of Internal Medicine Policlinico Foundation IRCCS University of Milan-Italy</td>
</tr>
<tr>
<td><strong>Miguel R Abboud, MD</strong></td>
<td>Medical Director, Professor of Pediatrics, Children’s Cancer Center of Lebanon, American University of Beirut Medical Center</td>
</tr>
<tr>
<td><strong>Hassan Abolghasemi, MD</strong></td>
<td>Head of Pediatric Hematology Oncology Society IBTO Managing Director Iranian Blood Transfusion Organisation (IBTO)</td>
</tr>
<tr>
<td><strong>Androulla Eleftheriou, PhD</strong></td>
<td>Executive Director, Thalassaemia International Federation, Cyprus</td>
</tr>
<tr>
<td><strong>Slaheddine Fattooum, MD</strong></td>
<td>Director, Research Laboratory of Molecular Biology, Tunis. President, Tunisian Association of Hemoglobinopathies and Thalassemia</td>
</tr>
<tr>
<td><strong>Mehran Karimi, MD</strong></td>
<td>Professor of Paediatric Haematology-Oncology, Nemazee Hospital, Shiraz</td>
</tr>
<tr>
<td><strong>Amenea Sadat Naghash, MD</strong></td>
<td>Paediatric Haematologist Chief of Thalassaemia Ward in Medical Centre for Special Diseases</td>
</tr>
<tr>
<td><strong>Kusai Al-Zir, MD</strong></td>
<td>Professor of Medicine – Pediatrics &amp; Haematology, Head Of Thalassaemia Patient's Friends Association And Hereditary Blood Diseases Syria</td>
</tr>
</tbody>
</table>
Organising Committee

Kusai Al-Zir, MD (Chairman)

Panos Englezos (Co-Chairman)
President, Thalassaemia International Federation, Cyprus

Mouna Haraoui
Member of the Board, Thalassaemia International Federation
President, Chronic Care Center, Lebanon

Fatemeh Hashemi
Member of the Board, Thalassaemia International Federation, Cyprus
President, Charity Foundation for Special Diseases, Iran

Anton Skafi
Assistant Secretary, Thalassaemia International Federation
Member, Thalassaemia Patients Friends' Society, Palestine

Faculty members

Miguel Abboud

Athanasios Aessopos, MD PhD
Associate Professor of Internal Medicine, University of Athens

Michael Angastiniotis, MD
Medical Advisor, Thalassaemia International Federation, Cyprus

Rekha Bajoria
Clinical Senior Lecturer in Medical Education (Obstetrics and Gynaecology) at Institute For Women’s Health at University of London, UK. Consultant Obstetrician, North Middlesex Hospital, London, UK

Amal El-Beshlawy, MD

Farid Boulad, MD
Associate Professor of Clinical Paediatrics, Weill Medical College of Cornell University, New York

Maria Domenica Cappellini, MD

Ratna Chatterjee, MD PhD
Clinical Senior Lecturer/Consultant in Reproductive Health, University College London/University College Hospital, London

Androulla Eleftheriou, PhD

Hussein A. Gezairy
Regional Director - WHO/EMRO, Egypt

Ardeshir Ghavamzadeh, MD
Director, Haematology-Oncology & BMT Research Centre, Tehran University of Medical Sciences

Mohsen A El-Hazmi, PhD
Ash Shura (Parliament) Member, Adjunct Professor, King Saud University College Of Medicine, Riyadh

Abdullah Al-Jefri MD
Head, Section of Haematology Department of Paediatric Haematology/Oncology King Faisal Specialist Hospital and Research Centre – Riyadh- Saudi Arabia

Mehran Karimi

Adlette Inati Khoriaty, MD
Head of Division of Paediatric Haematology-Oncology, Rafik Hariri University Hospital, Beirut. Consultant Haematologist, Chronic Care Centre, Beirut
Mary Petrou
Head of Perinatal Centre
University College Hospital NHS Trust
And Royal Free and University College
London Medical School
Perinatal Centre Department of Obstetrics and Gynaecology-London

John B Porter, MD
Professor & Consultant Haematology-
University College London Hospitals, UCL
School of Medicine

Mohamad Al-Shahrani, MB ChB
Consultant, Paediatric Haematology/
Oncology and BMT, Dept of Paediatrics,
Riyadh Armed Forces Hospital, Riyadh

Ala Sharara, MD
Professor, Department of Medicine,
Division of Gastroenterology, American
University of Beirut Medical Center

Ashraf TM Soliman, MD PhD
Head and Consultant Paediatric Endocrinologist, Hamad Medical Corporation, Doha, Qatar

Ali Taher, MD

Paul Telfer, MD
Consultant in Paediatric Haematology, St Bartholomew’s and The Royal London NHS Trust. Senior Lecturer in Haematology, Queen Mary, University of London

John Wood, MD PhD
Assistant Professor of Paediatrics,
Children's Heart Centre,
Children's Hospital of Los Angeles

Kusai Al-Zir, MD
Haemoglobin disorders in the Eastern Mediterranean Region

For decades haemoglobin disorders did not constitute a priority on the agenda of the World Health Organization. Resolution WHA 57.13 on genomics, adopted at the 57th World Health Assembly in 2004, and the 59th WHA in May 2006 formed an important milestone: the WHO urged its member states to focus attention and mobilise resources for action on control programmes for haemoglobin disorders and to prioritise them in their national health agendas.

Not only is there wide variation in the frequency of β-thalassaemia within the Eastern Mediterranean region, but there is also variation between geographical areas within the same country. The estimated carrier rates of β-thalassaemia in EMR countries range between 3–20%, while sickle cell disease is prevalent in only some areas, including parts of Saudi Arabia where carrier rates reach 12–13%.

Appropriate national registries and reliable, up-to-date epidemiological data are still lacking in many countries. Only in very few countries of the region, including Pakistan and Iran, has the economic burden of Hb disorders been documented. National control programmes, where they exist, are mostly ineffective. Reliable data is therefore urgently needed to provide evidence of the public health burden in order to develop or improve national control programmes. It is recognised that the development and maintenance of effective national control programmes rely heavily on political commitment and support.

Table 1: Basic demographic data for countries of the Eastern Mediterranean Region

<table>
<thead>
<tr>
<th>Country</th>
<th>Population thousands</th>
<th>Adult literacy rate % (age 15+)</th>
<th>Crude birth rate / 1,000</th>
<th>Infant mortality rate / 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>24,500</td>
<td>31 b</td>
<td>48.0</td>
<td>129.0 a</td>
</tr>
<tr>
<td>Bahrain</td>
<td>743 a</td>
<td>88 f</td>
<td>20.2</td>
<td>7.6 a</td>
</tr>
<tr>
<td>Djibouti</td>
<td>720 a</td>
<td>63 a</td>
<td>42.0 e</td>
<td>67.0 a</td>
</tr>
<tr>
<td>Egypt</td>
<td>73,435 a</td>
<td>61 a</td>
<td>25.3</td>
<td>33.2 a</td>
</tr>
<tr>
<td>Iran, Islamic Republic of</td>
<td>70,495 a</td>
<td>82 b</td>
<td>17.0</td>
<td>14.7 c</td>
</tr>
<tr>
<td>Iraq</td>
<td>29,000</td>
<td>65 a</td>
<td>37.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Jordan</td>
<td>5,600 a</td>
<td>91 a</td>
<td>29.0 b</td>
<td>19.0</td>
</tr>
<tr>
<td>Kuwait</td>
<td>3,328</td>
<td>94</td>
<td>17.3</td>
<td>8.6 a</td>
</tr>
<tr>
<td>Lebanon</td>
<td>3,928</td>
<td>Na</td>
<td>20.8</td>
<td>18.6 c</td>
</tr>
<tr>
<td>Libyan Arab Jamahiriya</td>
<td>5,419</td>
<td>86 d</td>
<td>20.3</td>
<td>21.5 a</td>
</tr>
<tr>
<td>Morocco</td>
<td>30,841</td>
<td>57 c</td>
<td>19.6</td>
<td>40.0 c</td>
</tr>
<tr>
<td>Oman</td>
<td>2,577 a</td>
<td>81 d</td>
<td>24.2</td>
<td>10.3 a</td>
</tr>
<tr>
<td>Pakistan</td>
<td>156,000</td>
<td>54 a</td>
<td>26.1</td>
<td>78.0</td>
</tr>
<tr>
<td>Palestine</td>
<td>3,762</td>
<td>94</td>
<td>36.7</td>
<td>24.2 b</td>
</tr>
<tr>
<td>Qatar</td>
<td>1,305</td>
<td>91 a</td>
<td>15.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>24,242</td>
<td>na</td>
<td>24.5</td>
<td>17.4</td>
</tr>
<tr>
<td>Somalia</td>
<td>7,960</td>
<td>25 a</td>
<td>44.6</td>
<td>86.0 a</td>
</tr>
<tr>
<td>Sudan</td>
<td>37,239</td>
<td>50</td>
<td>37.8</td>
<td>81.0 a</td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td>19,172</td>
<td>81 c</td>
<td>30.0</td>
<td>18.0 a</td>
</tr>
<tr>
<td>Tunisia</td>
<td>10,225</td>
<td>78 d</td>
<td>17.1</td>
<td>19.3 a</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>4,106 b</td>
<td>99 b</td>
<td>15.7</td>
<td>7.7 b</td>
</tr>
<tr>
<td>Yemen</td>
<td>21,535</td>
<td>53 d</td>
<td>39.7</td>
<td>68.5</td>
</tr>
</tbody>
</table>

Table 2: Studies on prevalence of sickle cell disease in the Eastern Mediterranean Region *

<table>
<thead>
<tr>
<th>Country</th>
<th>Population studied</th>
<th>% with SCD</th>
<th>% carrier of AS</th>
<th>S gene frequency</th>
<th>% SCD births predicted</th>
<th>Increase over expectation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>10327 neonates</td>
<td>2.1</td>
<td>11.2</td>
<td>0.077</td>
<td>0.59</td>
<td>X 3.6</td>
</tr>
<tr>
<td>Iraq (southern)</td>
<td>610 women</td>
<td>1.7</td>
<td>16</td>
<td>0.097</td>
<td>0.94</td>
<td>X 1.8</td>
</tr>
<tr>
<td>Lebanon</td>
<td>3000</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oman</td>
<td>952 247 cord blood</td>
<td>0.37</td>
<td>6.1</td>
<td>0.034</td>
<td>0.12</td>
<td>X 3.1</td>
</tr>
<tr>
<td>Saudi Arabia all country</td>
<td>9979 neonates</td>
<td>1.37</td>
<td>13.1</td>
<td>0.079</td>
<td>0.63</td>
<td>X 2.2</td>
</tr>
<tr>
<td>- Khaiber</td>
<td>580 children and adults</td>
<td>1</td>
<td>23.9</td>
<td>0.129</td>
<td>1.68</td>
<td>X 0.6</td>
</tr>
<tr>
<td>- Tehamat–Aseer</td>
<td>1582 children and adults</td>
<td>0.63</td>
<td>13.1</td>
<td>0.073</td>
<td>0.53</td>
<td>X 1.2</td>
</tr>
<tr>
<td>- Badr</td>
<td>377 children and adults</td>
<td>-</td>
<td>6.8</td>
<td>0.034</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Al-Qassim</td>
<td>1015 adults</td>
<td>-</td>
<td>0.197</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SCD: Sickle cell disease  
AS: Sickle cell trait  
* Note: This data is currently being reviewed and updated by EMRO WHO.

Common regional challenges

There are a number of important challenges that are common to the region, such as the tradition of consanguineous marriage; young marriage age; reservations about intervention during pregnancy; and a generally low education level of the populations. However, tangible improvements are taking place in many countries, particularly Syria, Lebanon, the Kingdom of Saudi Arabia and others.

The epidemiology of genetic disorders is especially complicated in the Eastern Mediterranean region because many whole villages or tribal groups are descended from a limited number of main ancestors. It is to be anticipated that some family groups have an unusual burden of haemoglobin disorders while others may not. It is important to identify carriers of the genes and inform them on how to reduce their genetic risk, while raising general awareness about carrier status in order to combat discrimination against carrier individuals. Genetic counselling services are therefore particularly important in the region, and genetic services should be strongly family-oriented.

The typical Eastern Mediterranean family structure contributes to the increase of incidence in recessively inherited disorders. Some 20-50% of marriages in many countries of the region are between blood relatives, compared to less than 1% in most European and North American countries. A marriage between first cousins is usually considered to about double the (approx. 2.5%) risk of having a child with a severe congenital or genetic disorder. In industrialised countries, recessively inherited disorders (1.66/1,000 births) account for less than 20% of single gene disorders and less than 5% of congenital and genetic disease. First-cousin marriage is considered to multiply the risk of recessively inherited disorders by 15–30 times, making the risk 25–50/1,000 and so doubling the total frequency of congenital and genetic disorders. Nevertheless, the risk remains relatively small and most consanguineous marriages have no adverse genetic effect.1

1 Source: Community control of genetic and congenital disorders (WHO EMRO, 1997)
Table 3: Estimates of frequency of haemoglobin disorders in countries of the Eastern Mediterranean Region *

<table>
<thead>
<tr>
<th>Country</th>
<th>% of population carrying:</th>
<th>Carriers (thousands)</th>
<th>Affected</th>
<th>Annual number born with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HbS</td>
<td>HbC</td>
<td>β-thal</td>
<td>HbE</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>493</td>
</tr>
<tr>
<td>Bahrain</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Egypt</td>
<td>3</td>
<td>3</td>
<td>1531</td>
<td>58</td>
</tr>
<tr>
<td>Iran, Islamic Republic</td>
<td>1</td>
<td>1–12</td>
<td>4</td>
<td>2230</td>
</tr>
<tr>
<td>Iraq</td>
<td>0–20</td>
<td>3</td>
<td>6</td>
<td>1175</td>
</tr>
<tr>
<td>Jordan</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>145</td>
</tr>
<tr>
<td>Kuwait</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>110</td>
</tr>
<tr>
<td>Libyan Arab Jamahiriya</td>
<td>2</td>
<td>1</td>
<td>1–2</td>
<td>4</td>
</tr>
<tr>
<td>Morocco</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>1671</td>
</tr>
<tr>
<td>Oman</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>Pakistan</td>
<td>+</td>
<td>+</td>
<td>2–6.5</td>
<td>+</td>
</tr>
<tr>
<td>Palestine</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>Qatar</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1–25</td>
<td>+</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>Sudan</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>1621</td>
</tr>
<tr>
<td>Syrian Arab Republic</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>779</td>
</tr>
<tr>
<td>Tunisia</td>
<td>2</td>
<td>+</td>
<td>3</td>
<td>460</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>Yemen</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>739</td>
</tr>
</tbody>
</table>


Values given in italics are estimates
+: Present (low frequency)
* Note: This data is currently being reviewed and updated by EMRO WHO.
Lack of prevention leads to spiralling cost of treatment
As paediatric services improve, and increasing proportion of affected children, who would otherwise have died of infection of heart failure in the first years of life, are diagnosed and require treatment. Treatment of haemoglobin disorders involves regular blood transfusions to maintain an adequate haemoglobin level and iron chelation therapy to remove excess accumulated iron from the body. Patients who are treated appropriately today have a very good prognosis. They can grow up to lead near normal lives, be educated, work and have families of their own.

Treatment, however, is complex and very costly. As treated children survive into adult life, the annual cost of treatment rises in direct proportion of the number of new affected infants diagnosed. When the annual number of affected births is known, reliable projections can be made regarding future requirements of blood and drugs for the management of both thalassaemia and sickling disorders.

In Pakistan, it is estimated that the average cost of iron chelation therapy per transfusion-dependent patient with β-thalassaemia major is USD 4,400, which is about 10 times the average annual income. The cost of treatment for one year of all the existing 1,200 patients equates to 4% of the government's health expenditure. In Iran, it has been estimated that in 2003 alone, some 25% of national blood products and 6 million vials of desferrioxamine were used for its registered patients.

Fulfilling the blood requirements of patients with haemoglobin disorders requires an adequate voluntary blood donation system. Lifelong iron chelation treatment is also very expensive. Bone marrow transplantation can offer a definitive cure but is only suitable to a small proportion of patients. The increasing burden of haemoglobin disorders, and other inherited disorders, on national health systems and families means that it is essential to implement effective prevention programmes.
**Table 4: Haemoglobin disorders in the EMRO Region**

<table>
<thead>
<tr>
<th>Country</th>
<th>Population thousands</th>
<th>IMR</th>
<th>Births/1,000 lbs</th>
<th>Estimated affected births /yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>22,500</td>
<td>165</td>
<td>647</td>
<td>1,078</td>
</tr>
<tr>
<td>Algeria</td>
<td>n/a</td>
<td>39</td>
<td>375</td>
<td>750</td>
</tr>
<tr>
<td>Bahrain</td>
<td>743</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Egypt</td>
<td>73,435</td>
<td>35</td>
<td>502</td>
<td>1,672</td>
</tr>
<tr>
<td>Iran</td>
<td>70,495</td>
<td>35</td>
<td>955</td>
<td>1,592</td>
</tr>
<tr>
<td>Iraq</td>
<td>29,000</td>
<td>107</td>
<td>1,235</td>
<td>823</td>
</tr>
<tr>
<td>Jordan</td>
<td>5,600</td>
<td>27</td>
<td>135</td>
<td>169</td>
</tr>
<tr>
<td>Kuwait</td>
<td>3,328</td>
<td>10</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Lebanon</td>
<td>3,928</td>
<td>28</td>
<td>41</td>
<td>69</td>
</tr>
<tr>
<td>Libya</td>
<td>5,419</td>
<td>16</td>
<td>88</td>
<td>146</td>
</tr>
<tr>
<td>Morocco</td>
<td>30,841</td>
<td>39</td>
<td>853</td>
<td>775</td>
</tr>
<tr>
<td>Oman</td>
<td>2,577</td>
<td>12</td>
<td>150</td>
<td>94</td>
</tr>
<tr>
<td>Pakistan</td>
<td>156,000</td>
<td>84</td>
<td>6,408</td>
<td>5,340</td>
</tr>
<tr>
<td>Palestine</td>
<td>3,762</td>
<td>21</td>
<td>106</td>
<td>132</td>
</tr>
<tr>
<td>Qatar</td>
<td>1,305</td>
<td>11</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>24,242</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Syria</td>
<td>19,172</td>
<td>23</td>
<td>792</td>
<td>495</td>
</tr>
<tr>
<td>Tunisia</td>
<td>10,225</td>
<td>21</td>
<td>246</td>
<td>176</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>4,106</td>
<td>8</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Yemen</td>
<td>21,535</td>
<td>30</td>
<td>1,525</td>
<td>953</td>
</tr>
</tbody>
</table>
Scientific Programme

The scientific programme ran over two days and covered the current state of art in the control of haemoglobin disorders, including prevention and clinical management, as well as the latest research data on gene therapy. The faculty was comprised of a number of national and international experts in the various specialities (see p.6). The European Haematology Association (EHA) accredited the conference with 12 CME units (see Annex 3).

Several abstracts were received for a poster presentation, which however did not take place due to lack of an appropriate space. These abstracts are included at the end of Annex 2.

The first session provided a picture of the current epidemiological status of haemoglobin disorders in the Eastern Mediterranean region. WHO/EMRO Regional Director Dr Hussein Gezairy gave the first overview.

Session 1: Epidemiology and Prevention in the Middle East Region

From Professor Gezairy’s presentation it was evident that the Middle East is a region where haemoglobin disorders as well as GGPD deficiency are highly prevalent and contribute significantly to infant mortality and morbidity. The economic burden of these disorders is high, and many patients do not receive treatment since the cost of iron chelation therapy alone in some countries amounts to many times the average annual income of a family. Prevention strategies are hampered by various cultural, religious and social factors, including low educational levels, customary consanguineous marriage, constraints on pregnancy termination, and by factors related to the lack of an appropriate health infrastructure. Pre-marital screening and genetic counselling are the focus of prevention in EMR. Legislation on pre-marital screening provides major step towards prevention and is mandatory in most countries of the region, although there are weaknesses in enforcement. In Bahrain, for example, the birth rate of babies with sickle cell has dropped to less than 1% following the implementation of pre-marital screening legislation.

A number of these issues were analysed by Professor Mohsen El-Hazmi of Saudi Arabia, who explained the ethical issues involved in effectively addressing prevention issues from the Islamic point of view. Ethical issues are particularly contentious in genetics because of the way genetics impinge on the individual, family and society. Islamic ethics emphasises the principles of autonomy of the person, beneficence, non-maleficence, fairness and equity, confidentiality and the responsibility of the doctor. There are no restrictions related to prevention of genetic diseases such as pre-implantation genetic diagnosis or premarital screening, but the usefulness of prenatal diagnosis is restricted because termination of pregnancy is allowed only in limited cases.

In a third presentation, Dr Mary Petrou described the contribution of pre-implantation genetic diagnosis (PGD) in achieving effective prevention. PGD technology has the advantage of avoiding the issues of pregnancy termination, which is unacceptable or undesirable in some countries. The method is still expensive and technologically demanding, but may have a valuable place in the prevention strategies of this region. Already the technology and expertise are available in several countries of the region, although PGD is still far from being integrated into national programmes.

Epidemiological data from Syria and Egypt were presented, demonstrating the very high prevalence of the disease in these countries and the pivotal role effective national prevention programmes are expected to play in the improvement of the quality of healthcare provided to patients.
**Session 2: Blood Transfusion**

The principles of blood transfusion therapy were discussed by Professor John Porter, who underlined the importance of improving the safety and adequacy of blood. Although the countries of the Middle East do not adhere to any specific directives, many of them have adopted aspects of European, international or American standards supported by WHO guidelines. The goals of blood transfusion, basic requirements, adverse reactions and recommended regimen were presented. New technologies for minimising infection risk were discussed, including pathogen inactivation as well as advancements in the production of red cells from human embryonic stem cells or from somatic stem cells.

Many countries of the region have difficulty in maintaining adequate quantities of blood for their patients, as well as implementing safety standards for optimising transfusion therapy.

Valuable calculations on the quantity of blood needed to raise Hb to recommended levels, and the amount of iron deposition from the transfused blood in the context of a standard transfusion regimen were presented. Prof. Porter stressed the importance of the close monitoring of transfusion requirements in the context of prompt hypersplenism diagnosis and the benefit of splenectomy.

**Session 3: Iron Overload Therapy and Survival**

As is often the case in thalassaemia conferences, the iron overload and chelation session was the most attended one, as minimising iron overload constitutes the cornerstone of thalassaemia management. Clinicians now universally recognise the key role played by iron chelation therapy in the survival and prevention of complications in thalassaemia. The session covered all aspects from pathophysiology, iron load assessment, monitoring, as well as current treatment options.

Professor Maria Domenica Cappellini gave an overview of the history and use of the three chelating agents, Desferrioxamine (Desferal), Deferiprone (Ferriprox, L1) and Deferasirox (Exjade). An update on the newest agent Deferasirox was given by Professor John Porter.

Survival, how it is assessed, the causes of death and the effect of chelation on survival were discussed by the speakers, including Dr Paul Telfer. The best results are achieved when chelation therapy is tailored to the individual patient’s needs, using all the options that are available today. Improved survival has been associated with effective iron chelation, availability of oral iron chelators, and better adherence to therapy, younger age at starting therapy, and very importantly with the development of a multidisciplinary care approach, as provided in specific expert centres. The graphs below show improvement in survival in Italy and Cyprus.

Survival of thalassaemia patients in Cyprus by birth cohort (Source: Dr M Angastiniotis and Dr P Telfer, c/o Thalassaemia International Federation):

**Session 4: Cardiac Complications**
Heart disease is a major consequence of iron overload in thalassaemia, affecting both quality of life and survival. In fact it is demonstrated to be the number one cause of morbidity and mortality in thalassaemia patients.

The conference was honoured by the presence of two of a small international group of cardiologists who have paid special attention to the problem of cardiomyopathy in thalassaemia major in their research and clinical practice - Professor John Wood and Professor Athanasios Aessopos. Their detailed analysis of all aspects of cardiac complications – including pathophysiology, prevention, early diagnosis and management, both in thalassaemia major and intermedia – has been invaluable. Both speakers emphasised early intervention as a means of preventing or minimising the development of serious heart disease. Reliable methods for monitoring and predicting the risk of iron deposition in the liver and heart were discussed, including assessment using Doppler Echo and tissue Doppler, Radionucleotide Cardiac Scan (MUGA), Cardiac Magnetic Resonance (CMR) imaging and use of B-type naturetic protein (BNP) measurements.

**Session 5: Sickle Cell Disease**
The first day ended with an important session on sickle cell disease, which is prevalent in many areas of the Middle East. Two experienced speakers from Lebanon, Dr Adlette Inati and Dr Miguel Abboud, analysed its pathophysiology, complications and management, including the role of hydroxyurea and of chronic transfusions especially in those at high risk for stroke. It was shown that in 33% of patients with sickle cell disease who developed iron overload it was due to blood transfusion therapy, while iron load was also seen in some patients who had not received transfusions. This strongly indicates that the iron status of patients must be monitored and effectively treated to avoid organ damage. The methods of assessment are the same as those used in thalassaemia. The National Institutes of Health (NIH) USA has recommended guidelines for the treatment of iron overload in sickle cell disease with Desferrioxamine in 2002, which include a serum ferritin level of >1,000μg/l and a liver iron concentration (LIC) of equal or greater than 7mg Fe/g dry weight. The use of Deferasirox in sickle cell disease was also described.
**Session 6: Endocrine Complications**

In the first session of the second day, presentations and discussions concentrated on endocrine complications in haemoglobin disorders, mostly iron-load associated but also treatment-related. Topics included growth, diabetes, bone disease, fertility and pregnancy. If complications are not appropriately addressed, they have a significant impact on the quality of life of patients. Various aspects were presented by Dr Ashraf Soliman, Dr Ratna Chatterjee and Dr Rekha Bajoria.

The speakers covered clinical, laboratory, radiological and other tools for early diagnosis, treatment and accurate monitoring of endocrine-related complications. Diabetes mellitus affects 20–30% of adult patients with β-thalassaemia and accounts for significant morbidity, so it received particular attention. The presenter focused on prevention and future tools, including imaging (MRI) and biochemical methods of monitoring in order to prevent the development of diabetes. Bone disease, including osteopenia and osteoporosis syndrome (OOS) was also discussed as it is observed in 70–80% of adult patients worldwide and constitutes a major cause of bone pain and fractures.

The causes of these complications, although not all known, include multiple endocrinopathies and genetic factors. The role of the Dexa scan, biochemical bone makers and histomorphometry in the establishment of diagnosis were discussed. Another focus was on research tools for current and future management of OOS, as well as the role of hypogonadism in the genesis of OOS, the scope and limitation of hormone replacement therapy, and the role of bishosphonate and other drugs in the management of OOS.

Dr Bajoria focused her presentation on current perspectives on fertility and pregnancy in thalassaemia. Pregnancy is now feasible for women with normal resting cardiac performance and optimised iron load status. The expectation to have a family is an important aspiration for a better quality of life and can today become a reality. It is essential that the patient adheres to good quality basic healthcare and optimal transfusion and chelation therapy. The majority of patients will need assisted reproductive techniques, due to hypogonadotrophic hypogonadism occurring in the majority of female patients.

**Session 7: Liver Disease in Thalassaemia**

Liver disease, with special emphasis on transfusion-associated hepatitis C infection, was presented by Professor Ala Sharara. Despite improved methods of detection and blood collection strategies (voluntary), it still remains a risk in this region, particularly where there is a high prevalence of carriers in the general population. This is a serious complication in thalassaemia since the infection may be compounded by transfusion-related hepatic siderosis whose treatment is demanding and very costly.

An update on current treatment protocols was given with particular emphasis on the increased need for blood and adjustment of iron chelation therapy as a consequence of the observed anaemia that is associated with the use of Ribovirin, one of the drugs given in combination with others for the treatment of HCV infection. Different types of responses and their observed levels in patients with thalassaemia was discussed. There is a need in this area for the compilation of more information and data on treatment protocols, as well as results from patients in different countries, so as to make safer conclusions on whether or not, and how, thalassaemia affects the pathogenesis of the viruses and the response to treatment.

**Session 8: Thalassaemia Intermedia**

Thalassaemia intermedia, previously regarded as a good prognosis category, is now known to bring serious complications in later life, often necessitating the initiation of regular blood transfusions and the use of effective iron chelation treatment to prevent the development of iron
load-related complications. Treatment protocols for TI should include reliable tools and methods of monitoring and diagnosing promptly iron deposition in the body.

The subject was introduced by Professor Maria Cappellini, who elaborated on its pathophysiology and treatment. Thalassaemia intermedia represents up to one fourth of β-thalassaemia patients and is characterised by a wide spectrum of different genotypes and a clinical phenotype ranging between severe, transfusion-dependent thalassaemia major and the asymptomatic carrier state. Professor A Aessopos presented the topic of heart disease in TI, which has a different etiology, pathophysiology and clinical presentation from thalassaemia major and it mainly manifests as age-related pulmonary hypertension (found in up to 60% of cases) and right-sided heart deterioration and failure. Early application of transfusion therapy combined with proper iron chelation may prevent cardiovascular injury.

Thrombosis in TI was presented by Professor Ali Taher. The high incidence of thromboembolic events in TI patients has led to the identification of hypercoagulability as a pathologic state in these patients. Diverse factors contributing to it have been identified. The main risk factors are age beyond 20 years, splenectomy, family history and previous thrombotic events. The reduction of thromboembolic events in adequately transfused patients may be the result of decreased numbers of pathological red cells. Based on intrinsic and extrinsic factors, it may be possible to design a thalassaemia-tailored thrombosis risk-assessment model to serve as a guideline for preventative treatment.

The case for the use of hydroxyurea in these patients was presented by Dr Mehran Karimi. Hydroxyurea could be a useful alternative to blood transfusion in some patients; more research is needed to define the criteria for predicting better which patients will best respond to this treatment.

**Session 9: Stem Cell Transplantation**

A definitive cure of haemoglobin disorders is possible through stem cell transplantation, fetal globin induction and gene therapy. Stem cell transplantation is limited by the need to have a fully histocompatible sibling donor, which seems to be available to around 20% of patients globally. However, in the Middle East the custom of consanguineous marriage increases the chances of having a family donor, so this method is particularly important here despite its financial and technological requirements.

The experiences of Saudi Arabia were described by Dr Abdullah Al Jefri, and of Iran by Dr Ardeshir Ghavamzadeh.

Dr Al Jefri described a study of 62 transplantations undertaken at the King Faisal Specialist Hospital and Research Centre between January 1998 and July 2006, where 60 patients were transplanted from HLA-matched donors. The overall survival was 94% and event-free survival 77%. Patients with mild disease and young age fared best and were least affected by graft versus host disease or rejection. The study also indicates that patients with Hepatitis C can be transplanted successfully provided they do not have active liver disease.

Dr Ghavamzadeh described the experience of the Hematology-Oncology and Stem Cell Transplantation Research Centre, at Shariati Hospital, Tehran over 18 years of transplantation. A total of 393 thalassaemia major patients have been treated, with an overall survival of 78.6% and disease-free survival of 68.5%. Acute GvHD occurred in 47% of patients and chronic GvHD in 24%. Better results were achieved in younger patients.
Session 10: Molecular Therapeutic Potentials

Fetal haemoglobin induction was presented by Professor Amal El Beshlawy. Thalassaemia patients do not become anaemic until fetal γ-globin genes are developmentally silenced. Patients with persistent high levels of fetal globin typically have less severe anaemia, milder clinical syndromes and are often transfusion independent. Reactivation of fetal haemoglobin could therefore benefit many patients. Prof El Beshlawy outlined the various pharmacological agents that have been studied, as well as the supportive measures that affect the activity of fetal globin inducers. Induction of HbF in thalassaemia patients is expected to be particularly important for developing countries that are unable to sustain the high cost of clinical management of thalassaemia patients.

The subject of gene therapy aroused particular interest, because it is known that one team in Paris has already started human trials, and a second team is planning a trial in 10 patients within this year.

The speaker, Dr Farid Boulad from the Sloan Kettering Cancer Center in New York, is a member of the latter team, which will start a phase I open-label clinical trial for the treatment of thalassaemia major using a lentiviral vector encoding the normal β-globin gene. Stem cells from the patient, transduced with the vector, will be returned to the patient via an autologous transplantation procedure using a non-myeloablative cytoreduction regimen. Dr Boulad explained in detail the principles, the project design and its aims. The objectives of the trial are to investigate safety and tolerability and the success of engraftment of the transduced CD311+ Cells and of course the expression of the transduced β-gene. On the side of safety, the monitoring of possible insertional oncogenesis will be a primary aim. The initial patient group will be 15 years or older patients with transfusion-dependent thalassaemia and an HLA-matched sibling. Patients with liver cirrhosis will be excluded, and a good cardiac function (EF ≥1.5mg/dl) will be necessary in all subjects. Any active viral infection as well as diabetes, pregnancy, epilepsy or a history of familial cancers will also be exclusion criteria. Patients will be fully and appropriately informed of the nature of the therapy and the requirements of the trial.

Session 11: Reference Thalassaemia Centres

The final talk of the scientific programme was given by TIF Medical Advisor Dr Michael Angastiniotis, who emphasised the role of expert centres for haemoglobin disorders in improving the quality of care, patient empowerment and self-management, and in developing research protocols.

Haemoglobin disorders are chronic disorders with multi-organ involvement and complications, requiring multi-disciplinary care. Specialised centres exist, but there are no standards designating a centre as an expert or reference centre. An important aspect is the contribution of the patient to the management of her/his condition, which will also help improve quality of life. Psychological and social support services should be integrated with medical services. In many countries, quality care has achieved the survival of patients well into adult life, mainly through good blood transfusion and iron chelation practices, but also by adopting follow-up protocols for monitoring, early detection and treatment of complications.

The focus of the talk was on the criteria to be used for establishing an expert centre. Such criteria are currently being discussed in Europe in order for European centres to acquire consistent quality services. The existence of reference centres is essential in every affected country or region, so that patients can be referred and receive expert opinion and follow-up, and so that multi-care support can be provided. This is particularly important in countries of the Middle East, where a multi-disciplinary approach is almost absent from hospitals and centres treating patients with haemoglobin disorders.
There are two main sets of standards which can serve as starting points in developing standards or criteria for haemoglobinopathy centres: in Europe, a set of suggested criteria has been developed by the European Commission’s Rare Disease Task Force (2006), and in the USA, the Chronic Care Model developed by Dr Wagner of the McColl Institute in Seattle. Dr Angastiniotis went on to list and explain the various criteria. In addition, a useful guide is provided in chapter 17 of the Guidelines for the Clinical Management of Thalassaemia, 2nd ed. revised (TIF, 2008). Recognising these standards is necessary not only for health planners and providers, but also for patient support organisations. There are questions as to whether these ideal standards are achievable in all countries and in all contexts; but quality of care is an ethical requirement in any setting and in any country.
Patients and Parents’ Programme

The patients/parents’ programme forms an essential part of all TIF’s educational events. It allows patients and their family members to receive up-to-date information about optimal treatment, delivered by international experts in a patient-friendly format, but also gives opportunities for patients and parents to ask questions of the experts, and for patient groups to discuss specific issues. Peer support and networking are also important aspects of the patients’ programme.

The patients’ programme in Damascus ran over one day, allowing the opportunity for patients to attend some of the scientific sessions on the first day if they wished. The sessions covered clinical management and other vital issues touching on patients’ live, such as psychosocial concerns and patients’ rights.

**Session 1** covered blood transfusion and iron chelation, with talks given by Professor Maria-Domenica Cappellini and Dr Paul Telfer. The expert speakers summarised for patients the state of art of new chelators and of different chelation regimens. They answered to specific questions from the audience.

**Session 2** covered cardiac complications and thalassaemia intermedia, with presentations by Professors Ali Taher, John Wood and Athanasios Aissopos. These topics have been already summarised in the scientific programme pages above.

**Session 3 – Endocrine and hepatic Complications**
This session covered the topics of growth, fertility, osteoporosis, diabetes and chronic Hepatitis.

Dr AT Soliman presented issues related to growth. Retarded growth occurs almost invariably in β-thalassaemia patients, although in recent years growth has improved markedly with high transfusion regimes and efficient iron chelation. Dr Soliman outlined the major causes of growth retardation, including haemosiderosis – damage to the endocrine glands – and other factors. Recommendations for thalassaemia patients include paying attention to the quality and quantity of nutrition, vaccination against Hepatitis B, and closely monitored growth hormone therapy. Early treatment is essential.

Fertility and pregnancy were covered by Dr Rekha Bajoria, who advised the patients that pregnancy is feasible for women with β-thalassaemia who have normal resting cardiac performance and optimised iron overload status. With proper multi-disciplinary specialist care, women with thalassaemia major can have successful pregnancies.

A talk on Osteoporosis was given by Dr Ratna Chatterjee, who also covered diabetes. Bone disease is a major cause of pain and bone fragility for thalassaemia patients: it is found in 70-80% of adult patients and has multiple causes, including bone marrow expansion, delayed puberty, use of chelation agents, and endocrinopathies. Diabetes is a major endocrinopathy that occurs in thalassaemia as a result of transfusional haemosiderosis and is found in 20-30% of adult patients. It is distinct from type 2 diabetes.

Dr Ala Sharara talked about the treatment of chronic Hepatitis B and C, outlining the various treatment options and factors that patients should bear in mind if infected with hepatitis.
Session 4 – Psychosocial Support and Social Integration

In this session, the patients themselves led the discussion.

Anton Skafi, a TIF Board member, presented psychosocial problems from the perspective of adult and older patients. Today, with appropriate treatment, most patients will live long into adulthood and the problems they face are quite distinct from children or young patients. Many patients who are today middle-aged, did not receive adequate treatment in childhood due to lack of awareness and unavailability of effective treatment, a situation resulting in many medical complications.

In addition to anxiety about future health, there are a number of other important concerns including employment and family. Anton Skafi gave advice deriving from his very personal experience to care givers on how to build trust and a partnership with the patient, and to families, teachers and employers on how to encourage patients to live full lives – underscoring at the same time the patients’ own responsibility to look after themselves and sustain a positive attitude.

Louis Pericleous, another patient, also member of the Board, presented social integration. One of the most important factors in successful integration of thalassaemia patients into society is appropriate healthcare. Patients when treated optimally, feel well, have less medical complications and fewer of the physical deformities characteristic of thalassaemia and which can have a psychologically and socially debilitating effect. It is also important that social support services are integrated into medical care, to address concerns about education, employment and family life. In Cyprus for example, where access to university was specially facilitated, patients have gone on to obtain professional qualifications and build successful careers.

Patient-government relations and patient-doctor relations were covered by Fatemeh Hashemi and Riyad Elbard, both TIF Board members. Mrs Hashemi explained the Iranian public health and healthcare systems, emphasising that healthy individuals are the building blocks of sustainable development in society, and that health is a fundamental right for all. The main message of both speakers was that building a collaborative relationship with government is essential for patients’ associations, as progress can only come about through political commitment. Patients’ associations therefore need to become professional and well organised, with the aim of involving themselves in policy-making on from initial planning to implementation.

Dr Androulla Eleftheriou, Executive Director of TIF, gave a talk on the importance of every patient recognizing and knowing well that they have rights as patients and they need to ask for them. Patients’ rights are based on the concept of the person and the fundamental dignity and equality of all human beings, as formalised in the 1948 Universal Declaration of Human Rights. Dr Eleftheriou stressed the empowerment of patients and the important role of information on the disease, its treatment and prevention. Patients’ associations play a crucial role as providers of up-to-date, reliable and unbiased information to patients. She also recommended that every country should develop a national patients rights’ charter, and indeed the example of Europe could be used as a good base.

Patients’ involvement in healthcare reforms is essential, and it is increasingly recognised that patients are becoming partners in decision-making regarding their treatment and their lives.

In the final discussion and “personal story” session, Rayan Samad from Lebanon spoke about his life experiences. Like most patients, in his experience adversities – constant worries about health and the pains of medical treatment – mingle with positive feelings – family support and love, friendships and growing stronger as a person. Rayan, too, stressed the importance of maintaining an active life despite medical treatment.
Status of Patient Care in Participating Countries

Part 1: Medical Professionals

Analysis of health professionals’ questionnaires

Ninety health professionals from the participating countries responded to a questionnaire prepared by TIF and sent to all delegates (see annex). The respondents’ countries of origin were Syria, Iraq, Kuwait, Oman, Egypt, Saudi Arabia, Bahrain, Jordan, Yemen, Qatar, Algeria, Lebanon, Morocco and Iran. Of the participating health professionals, 86.8% came from the public sector, 5.7% from the private sector, and 7.5% belonged to both. They were selected solely according to their level of involvement in the treatment or prevention of Hb disorders in their respective countries.

The respondents were broken down by speciality as follows:

- Adult haematologists: 39.6%
- Paediatricians: 26.4%
- Paediatric haematologists: 20.8%
- Scientists: 7.5%
- Cardiologists: 1.9%
- General practitioners: 1.9%
- Nurses: 1.9%

Of the respondents, 86.8% were attached to public health hospitals or medical centres, 3% to private centres, and 4% had attachments to both sectors. Collectively, the 90 doctors provide clinical management to 11,370 patients in 35 clinics across the region.

Nearly all (98.4%) stated that educational conferences and workshops are their preferred method of receiving professional updates. 94.6% of the respondents had attended at least one TIF educational event in the past, and 62.8% had attended more than one.

Further, almost all 96.4% confirmed the use of TIF’s educational publications for updating their knowledge, mainly referring to the *Guidelines for the Clinical Management of Thalassaemia*.

86.4% of respondents reported poor or lack of multidisciplinary support to their work, and cited the absence of centres of expertise as the most significant constrain in the delivery of quality care to patients. Also, 10.5% reported that limited national resources prevented the maintenance of sufficient supplies of iron chelation drugs.

When asked regarding the availability of iron chelation drugs, 82.5% said they would prefer to have all three available drugs at their disposal, either reimbursed or provided free of charge by the government. 65.5% expressed interest to have more patients receiving Deferiprone, and 92.2% the new oral iron chelator Deferasirox. Of those who were prescribing Deferasirox, 94.8% reported a measurable increase in patients’ adherence to treatment – in 98% of patients receiving Deferasirox.

**Prevention**

National prevention programmes are lacking in the region, with the exception of Bahrain and Iran (national programmes fully implemented) and Saudi Arabia (some aspects of prevention in place). Although the technology and expertise may be present in some of the countries, the national health authorities have not yet proceeded to a strategy of designating quality...
laboratories for screening, prenatal diagnosis or preimplantation genetic diagnosis (PGD). The establishment of effective prevention is hampered in these countries mainly by reservations regarding the termination of pregnancy at 11 or more weeks after CVS prenatal diagnosis. A large percentage (>80%) wish to move towards PGD technology to overcome this cultural and religious barrier, because prenatal diagnosis in the absence of pregnancy termination will have very little, if any, impact on preventing affected births.

However, PGD technology is still very costly and technologically advanced. Should these countries decide to implement it, the necessary expertise must be gained and sufficient resources allocated by the governments. Other aspects of prevention, including community awareness, education of carriers, genetic counselling, etc. are also required to expand and strengthened a prevention programme. Even so, they alone cannot make a significant impact on prevention because all these aspects need to be encompassed within a national programme integrated at the level of primary healthcare, with strong government support.

Clinical management
Participating health professionals from 12 countries (Saudi Arabia, Algeria, Morocco, Yemen, Tunisia, Syria, Jordan, Egypt, Lebanon, Iran, Palestine and Bahrain) were asked questions on specific aspects of treatment of thalassaemia major/intermedia. The answers yielded the following information.

- The costs of treatment for blood transfusion and iron chelation are totally covered by the government in 10 countries and almost totally in 11 countries.
- Blood supplies are adequate throughout the year in 7 countries, with problems in 3 and severe problems in 2 countries.
- 100% voluntary, non-remunerated blood donation is not practiced in any of the countries, although such practices exist to a certain extent or are being promoted in many of them.
- All three available iron chelation drugs, i.e. Desferrioxamine, Deferiprone and Deferasirox are registered and available to patients in only 8 countries.
- Only two of them – Desferrioxamine and Deferasirox – are available in 3 countries, and only one – Desferrioxamine – in one country.

With regards to reference centres providing multidisciplinary care dedicated to patients with haemoglobin disorders, only 2 countries can be considered to have one such centre each. However, in most countries a tertiary unit in a hospital (one country), a department in university hospital (in two), or hospital units with paediatric or haematology departments are assigned as centres of “reference” or “experienced centres” in the treatment of Hb disorders.

A multidisciplinary care approach, with provision of regular checks and monitoring is poor or lacking, and even where services may be improved the ratio of reference centres to patients is far too low to be adequate. Non-nationals are not given free treatment in most countries of the region. All residents of Syria receive free treatment and some development in this area is also being achieved in Saudi Arabia.

The average age of patients with β-thalassaemia major was reported as follows:

- 16 years in four countries
- 20 years in three countries
- 10 years in five countries

In no country is the average age of patients above 25, and in most of them (75%) it is below 18 years.
Status of Patient Care in Participating Countries

Part 2: Patients’ Perspective

A specific patient questionnaire was prepared by TIF office to analyse the status of patients in the participating countries. This questionnaire was answered by 96 (69%) of the 140 patients who attended the conference from 12 countries: Syria, Saudi Arabia, Tunisia, Egypt, Lebanon, Yemen, Jordan, Iraq, Bahrain, Iran, Morocco and Algeria. Their characteristics were as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Nr. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–15</td>
<td>30</td>
<td>31.3</td>
</tr>
<tr>
<td>16–20</td>
<td>22</td>
<td>22.9</td>
</tr>
<tr>
<td>21–25</td>
<td>22</td>
<td>22.9</td>
</tr>
<tr>
<td>26–30</td>
<td>14</td>
<td>14.5</td>
</tr>
<tr>
<td>31–35</td>
<td>4</td>
<td>4.2</td>
</tr>
<tr>
<td>36–40</td>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>40 +</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Nr. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassaemia major</td>
<td>70</td>
<td>72.9</td>
</tr>
<tr>
<td>Thalassaemia intermedia</td>
<td>15</td>
<td>15.6</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>7</td>
<td>7.3</td>
</tr>
<tr>
<td>Not stated</td>
<td>4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

A. Clinical information on transfusion frequency

1. Thalassaemia major patients:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Nr. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 2 weeks</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>Every 3 weeks</td>
<td>10</td>
<td>14.5</td>
</tr>
<tr>
<td>Every 4 weeks</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>4 – 6 weeks</td>
<td>1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

2. Thalassaemia intermedia patients:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Nr. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 2 weeks</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Every 3 weeks</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Every 4 weeks</td>
<td>8</td>
<td>61.5</td>
</tr>
<tr>
<td>Other (sometimes)</td>
<td>1</td>
<td>7.8</td>
</tr>
</tbody>
</table>

3. Sickle cell patients:

Of the seven patients, two were not transfused, three received blood every 3 months, two irregularly between 3 and 12 months, and one case was on weekly transfusion. Seven patients did not answer.
B. Type of blood received, knowledge of pre-transfusion Hb levels, and iron chelation therapy

Blood product transfused:
Of the respondents, 78% received packed red blood cells, 41% received filtered, and only 12% packed, filtered and washed red blood cells.

Is pre transfusion haemoglobin measured and recorded?
Of the respondents, 80% said they knew their pre transfusion haemoglobin, with 64% of them being able to quote the number.

Iron chelation therapies used
Six patients did not answer this question. These included two sickle cell patients, one who did not state a diagnosis, and three patients from Yemen.

<table>
<thead>
<tr>
<th>Chelating agent</th>
<th>Nr. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferasirox (Exjade)</td>
<td>38</td>
<td>42.2</td>
</tr>
<tr>
<td>Desferrioxamine (Desferal)</td>
<td>29</td>
<td>32.3</td>
</tr>
<tr>
<td>Deferiprone (Ferriprox) monotherapy</td>
<td>6</td>
<td>6.6</td>
</tr>
<tr>
<td>Combination</td>
<td>17</td>
<td>19.0</td>
</tr>
</tbody>
</table>

C. Multidisciplinary care

Questions about endocrine and cardiac complications were used to assess the use of a multidisciplinary approach to address the needs of patients.

Monitoring of endocrine complications.
62.4% of patients reported that they had not seen an endocrinologist for several years. Only a third (33.3%) reported 3–6-monthly follow-ups. 3.6% reported seeing an endocrinologist once in a period of more than one year, and only 1% reported being seen by an endocrinologist every year.

Monitoring of cardiac complications
The situation appears somewhat better for cardiac follow-up, with 51.5% of patients reporting being seen by a cardiologist on a 3–6 monthly basis, 10% once a year and 9.3% once in a period of more than one year. However, 29.2% reported not having seen a cardiologist at all for many years.

D. Social and psychological issues

The following are some typical responses received from patients regarding social and psychological issues, including education, employment and psychosocial support.

School / education
The vast majority of patients go to school, with only 11 stating that they could not attend. Not all gave reasons for this, but some of the answers include:
• “Difficulty walking”
• “Lost too many days”
• “Teachers don’t care about the sick”
• “Always tired”
• “Palpitations”

24 patients went to school but did not graduate. Again only a few gave reasons, which included:

• “Was in hospital during exams”
• “Did not get grades”
• “Because of the disease”
• “Exhaustion after transfusion”
• “Could not secure success”

The majority (83%) intend or wish to go to university, with only 16% stating that they do not wish to. Of those that did not wish to, reasons were only given by four patients:

• “Hepatitis B infection”
• “Because of transfusions”
• “Because I could not continue”
• “I cannot”

Employment

To the question “Do you intend to go to work?”, the vast majority (83.3%) answered positively, with only 4% stating they do not intend to work and 12 not responding. The patients who did not wish to work gave the following reasons:

• “Poor health”
• “Work does not help, learning does”
• “Because I am sick”

Despite the intention to work, patients face obstacles – from employers, society and the disease itself. Only 19.8% of respondents felt there was no problem in getting a job. Of those who said had no problem finding work, characteristic statements include the following:

• “I got the job because of my intelligence”
• “No-one should refuse out of sympathy”
• “The law says to give priority to thalassaemics in employment”
• “Help comes from the thalassaemia association and the Ministry of Health”
• “Any employer understands”

However, difficulties with employers are frequent: 30.2% of patients stated that employers are reluctant to employ patients, while 11.4% stated that there is blatant refusal. Some patients (9.4%) felt that the difficulty was regarding the general shortage of jobs in their countries, and not just because of thalassaemia. The reasons given for employers’ reluctance or refusal included the following:

• “They think it (thalassaemia) is catching”
• “Repeated absences”
• “Fear that something is going to happen because of the disease”
• “They think that we can’t do the job”
• “Short height”
• “Difficult to get a job if features, facial or skin colour are obvious”
Some patients (7.3%), actually stated that they themselves could not or would not work. The reasons they gave included:

- “Long hours”
- “Transfusion is exhausting”
- “Limited tolerance for work”
- “Work needs big physical effort”
- “I get tired and sleepy”

18.75% did not answer this question, and three stated they did not know. 80.2% stated that they are healthy and strong enough to have a full time job, while (12.5%) felt they were not fit because:

- “Not strong enough”
- “Work makes me tired”
- “Depression”
- “Weak body”
- “Palpitations”
- “Backache”
- “Poor health”
- “Osteoporosis”

**Psychosocial support**

When asked whether they receive psychosocial support, 64.6% of the patients said yes, 30.2% said no, and 5.2% did not answer. However, when asked who provides this support, the majority felt that it came from the social environment rather than professional help.

Social sources of support:

- Support from immediate family, especially parents (mentioned by 27 patients)
- Support from friends (13)
- Support from relatives (13)
- Support from other patients (3)
- Support from the thalassaemia association (5)
- Support from the employer (1)
- One patient felt that meeting with other patients in conferences also gave support.

Professional sources of support:

- Doctor (8)
- The thalassaemia centre in general (7)
- Social worker (6)
- Nurses (1)
- Other staff, not specific (2)

**Social integration**

When asked whether they felt they were well integrated into society, 67.7% of the patients felt that they were, while 10.4% said they were but with some reservations, expressed as
“sometimes” or “partial” or “there is still some fear and caution”, or “I tell no one about my disease”.

Poor integration was expressed by 11.5% of patients, with statements such as “people look down on us”, “lack of awareness”, “because of my health”, “there is prejudice”. The age range of the patients who responded was 16–25 years. 10 patients did not respond to this section.

One patient stated that “it is the individual who proves himself, recognition does not come from others”. It seems that expert and well-adjusted patients may be able to offer valuable help to other patients.

**Major problems perceived by patients**
The patients were asked to define what they considered to be the most important problems in their lives. The main finding from this question is that most problems cited by patients concern personal fulfilment and not the disease directly, apart from the very common feeling of uncertainty and fear of the future. Work and family life seem to be clearly the most common concerns. Education and the availability of treatment are also mentioned often.

- Securing work, issues of employment (mentioned 26 times)
- Uncertainty and fear of the future (26)
- Marriage / finding a partner, someone to love (24), having children (3), pregnancy (3)
- Issues related to education, school, exams, going to university (11)
- Availability of treatment (10)
- Financial problems, lack of money (5)
- People’s comments, uncomfortable in the community (3)
- Family and other social problems (4)

More specific issues related to thalassaemia and its treatment include the following, with most being related to the availability and safety of blood transfusions:

- The quality of blood and the possibility of transmission of disease (11)
- Lack of a final cure (7)
- Feeling exhausted after transfusion (5)
- Short stature and deformity (4)
- Feeling generally exhausted (4)
- Pains and osteoporosis (4)
- Blood supply (3)
- Lack of sexual maturation (3)
- Splenomegaly / splenectomy (3)
- Lack of appropriate tests (3)
- Lack of blood bags (1)

Individual patients mentioned iron overload, heart and liver complications, lack of a donor for bone marrow transplantation, treatment with Desferrioxamine, lack of a chelation agent without toxicity, hospitalisation, surgery, needle pricks, lack of a specialised centre, and long intervals between medical appointments 19 patients (19.8%) did not answer the question.

**Belonging to an association**
Of the 96 patients who responded, 69 (71.9%) declared themselves members of a thalassaemia association. 22.9% do not belong to an association, and 5.2% did not answer.
When asked the question “How does the association help?”, the most frequent response was that the association secures or supplies treatment – mainly chelating agents. Only one patient explained that this was by cooperation with the government, so most respondents give the impression that the association is the primary provider. Only 3 patients mentioned activities in blood donation. The next most frequent service mentioned is recreational activities, trips and picnics, which patients seem to value very much: “They help us forget our problems”.

Psychosocial and moral support and patient education were also mentioned by several patients, while some individuals mentioned financial support and help in sending a patient to Italy for bone marrow transplantation. Only 2 patients responded that the association does not help at all. Another 2 said that is it currently too weak but improving. One patient could not see the point of an association, since the government provides all!

Patients’ expectation from TIF
Patients were last asked to describe the kind of expectations they have from TIF. Here are some of the most common answers:

- Develop further its educational programme for patients (72%)
  - “I want to know all about my disease”
  - “I wish to know more to discuss things with my doctor”

- Work closely with the national health authorities to inform them of the latest advancements in treatment (60%)
  - “I want to be like anyone else so that I can be loved”
  - “My association can help me with the support of TIF”

- Support the purchase of medicines for their treatment, i.e. iron chelation drugs (25%)
  - “I want to live as a normal person”
  - “I want to take my medicines regularly”

- Provide psychosocial support (16%)
  - “What about my life after five years? Marriage, children, love?”
  - “TIF must provide answers and solution to these”

- Creation of employment opportunities in their country (8%)
  - “We hope you find us jobs “
  - “I want to be a doctor”

- Support bone marrow transplantation for a cure (6%)
  - “BMT is my biggest dream”
  - “TIF must help”

- Secure safe blood, etc. (4%)
  - “I am very afraid of having hepatitis”
  - “TIF must help us with filters and .... to test blood”

Miscellaneous feedback and statements received from the patients included:

“Patients should be considered as handicapped and receive all associated benefits”
“A thalassaemia person should not be treated as a sick person”
“TIF to be for the whole world”
“Thank you very much!”
Conclusions and recommendations

In the Eastern Mediterranean region there are certain needs and weaknesses common to almost every country, albeit to a variable level. Those that have been identified as being in common include the following:

National prevention programmes

These need to be urgently developed and/or strengthened. Only two countries (Iran and Bahrain) have been successful in developing and implementing effective prevention with outstanding results. They could constitute a model for others to follow. Pre-marital screening legislation has been effected in several countries (e.g. KSA, Bahrain, Jordan) but there are remaining weaknesses in the enforcement of the legislation. Countries in the region should tailor the programmes to their specific needs, cultural factors, existing health infrastructures and available resources. Pre-marital screening programmes should be accompanied by appropriate genetic counselling to enable couples to identify and follow the most suitable reproductive option, as well as education of the public regarding the health status of carrier individuals, in order to avoid stigmatisation and discrimination. Prenatal diagnosis in Islamic countries carries the dilemma of termination of pregnancy, which is allowed only in limited circumstances. PGD technology can therefore offer a viable solution to circumvent such ethical problems. Expertise in the area of PGD exists in almost every country of the region, but co-ordination and assignment of areas of responsibility are lacking, pending political commitment.

The development of services for effective prevention necessitates the active political commitment and involvement by the government for securing the quality and sustainability of services. Reliable, up-to-date epidemiological data is still needed in some parts of the region to support better planning, as well as consensus on the methods and technologies to be implemented to address social, cultural and religious factors in achieving effective prevention.

Reference centres / centres of excellence

There is a lack of designated reference centres, or centres of excellence in the countries of the region, which directly affects the access of patients to quality clinical management. Reference laboratories are also needed for the implementation of effective prevention programmes.

Only two countries (Lebanon and Bahrain) have focused efforts and resources on this. In the majority of the rest (Jordan, Tunisia, Morocco) there are hospital or university departments (Saudi Arabia, Egypt) or centres (Syria, Iran, Bahrain) that treat and provide basic treatment to a satisfactory level with a need to focus on improving the quality and range of available services.

Networks of medical specialists and patients’ associations

There is a general absence of effective networks among patients’ associations and between patients’ associations and doctors. To encourage such networking and collaboration, TIF will aim to establish a Middle East Network of Patients and Medical Specialists in the field of haemoglobin disorders. The first such regional network was recently launched in Europe and will serve as a pilot before establishment of other regional networks.

The aims of such a network are to improve awareness among medical professionals about haemoglobin disorders; to gain a more accurate picture of the available services and any existing problems; to gather up-to-date epidemiological information, including numbers and locations of patients in the region; to raise awareness among patients and parents of the
existence of an international support network and peer groups in other countries; and to create networks of collaboration and close contacts between patients and medical professionals within and between countries. Through the collection of data a solid evidence base will be built to help focus TIF’s activities on the special needs of the region, but also to support EU and WHO efforts towards the creation of recommendations and guidelines for Hb disorders.

**Recommendations and next steps**

The goal and focus of activities should be to establish optimal treatment for patients, as well as effective prevention with minimal affected annual births, across the region.

1. This regional conference should be repeated every 2 years

2. National workshops with both professional and association meetings running in parallel are invaluable, both to improve knowledge and awareness, but also to improve collaboration between stakeholders. Another advantage is that service deficiencies in both case management and prevention are brought to the surface and may lead to the adoption of a corrective action by policy adjustments and action plans. TIF will support annually:
   a. a specific number of medical/scientific specialists from each country (according to the needs) to participate in educational workshops organised by TIF.
   b. the organisation of workshops/camps for patients associations to empower patients, educate them of their rights, role in promotion of their interests, ways to collaborate effectively and productively with health authorities and how to strengthen the psychosocial support of the patients.

3. A Regional Network as described above, to build close and effective communication between the associations and the TIF, as well as between associations and medical specialists. This will help to maintain awareness and action and give TIF early warning on important issues that require interventions. Three-monthly reports or other means of communication (videoconferencing?) will become the norm in this region.

4. Collaboration initiatives and maintenance of close communications between TIF, the ministries of health, national blood banks, the Middle East Thinkers’ Group, national thalassaemia associations, and WHO in each country to:
   a. encourage development of prevention and treatment protocols
   b. support programmes for training and education of scientists and health professionals
   c. establish whether blood needs are met and adequate standards applied
   d. promote the establishment of reference centres.

5. Maintenance of a Country Report on each country of the region based on the information collected during the first Pan-Middle East Conference. This report should be made available to each member association and the health authorities. It should also be annually updated at the TIF office according to latest information received in correspondence with the associations.

6. Establishment of an “Elite Circle” in the region for the promotion of haemoglobin disorders on national health agendas and fundraising for research projects. This will aim ultimately to become a global Elite Circle.
Three-year plan for countries in the EMRO region

The plan below represents a general outline, since each country has its own characteristics such as the level of services, resources, expertise, etc. There are 22 countries in this region with a total population of around 500 million. TIF should follow a plan for each country, which should have the following elements:

<table>
<thead>
<tr>
<th>Goal</th>
<th>Year 1 2009–2010</th>
<th>Year 2 2011</th>
<th>Year 3 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ensure the presence of at least one active association – weak in some areas (e.g. Algeria, Yemen) and strengthen existing ones across the region</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Delegation visit and meetings with Ministry of Health and local services providers and the association in needy countries</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Preparation of individual country report and recommendations once local needs are fully identified</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Ensure all TIF publications are all available in the local language (Arabic, Farsi, Urdu)</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Establishment of a focal point in each MoH for frequent communication – support and lobby for prevention, registries and treatment according to TIF’s Guidelines, and for more epidemiological studies</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>National workshops as described above, where necessary</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>7.</td>
<td>Support association members to attend TIF conference</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>8.</td>
<td>Promotion of the establishment of expert centres in as many countries of the region as possible according to international standards</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>9.</td>
<td>Establishment of national scientific committee to assist the MoH in planning strategies and setting goals</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>10.</td>
<td>establishment of a network of national and regional experts</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>11.</td>
<td>Establishment of an international twinning programme for health professionals or between centres</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>12.</td>
<td>Establishment of a regional Elite Circle</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Annex 1: Conference programme

1st Pan-Middle East Conference on Haemoglobinopathies
Damascus, Syria 1–2 May 2009

Scientific Programme
Day One – Friday 1 May 2009

09.00 – 09.10  Kusai Al-Zir (Syria) – Chairman
09.10 – 09.20  Panos Englezos (Cyprus) – Co-Chairman, TIF President
09.20 – 09.30  Ali Taher (Lebanon) – President of the Scientific Committee

Session 1 – Epidemiology & Prevention in the Middle East Region
Chairpersons: Hussein A. Gezairy (Egypt) and Mohsen El-Hazmi (Kingdom of Saudi Arabia)
09.30 – 09.45  Prevention and control of haemoglobinopathies in the Middle East region – Hussein Gezairy, Director WHO/EMRO
09.45 – 10.00  Ethical issues on prevention and management: Islamic point of view – Mohsen A El-Hazmi (Saudi Arabia)
10.00 – 10.30  Pre-implantation genetic diagnosis – Mary Petrou (UK)

Chairpersons: Slaheddine Fattoum (Tunisia) and Amal El-Beshlawy (Egypt)
11.00 – 11.15  Prevention of haemoglobinopathies in Syria – Kusai Al-Zir (Syria)
11.15 – 11.30  Prevention of haemoglobinopathies in Egypt – Amal El-Beshlawy (Egypt)
11.30 – 11.45  Prevention of haemoglobinopathies in the Kingdom of Saudi Arabia – Mohamad Al-Shahrani (Saudi Arabia)

S2 – Blood Transfusion

S3 – Iron Chelation Therapy
Chairpersons: Maria-Domenica Cappellini (Italy) and Paul Telfer (UK)
13.30 – 13.50  Pathophysiology of iron overload – John B Porter (UK)
13.50 – 14.10  Iron overload: consequences, assessment, and monitoring – Ali Taher (Lebanon)
14.10 – 14.40  Iron chelation: treatment with Desferrioxamine and Deferiprone – Maria-Domenica Cappellini (Italy)
15.10 – 15.30  Update on survival in thalassaemia – Paul Telfer (UK)

S4 – Cardiac Complications
Chairpersons: Kusai Al-Zir (Syria) and John B. Porter (UK)
16:00 – 16:30  Cardiac complications in thalassaemia major – John Wood (USA)
16:30 – 17:00  Assessment and treatment of cardiac iron overload – Athanasios Aissopos (Greece)

S5 – Sickle Cell Disease
17:00 – 17:30  Pathophysiology of sickle cell disease – Miguel Abboud (Lebanon)
17:30 – 18:00  Current understanding in the management of sickle cell disease – Adlette Inati-Khoriaty (Lebanon)
18:00 – 19:00  Case presentations and interactive discussion – John B Porter / Ali Taher / Maria-Domenica Cappellini
Day Two – Saturday 2 May 2009

S6 – Endocrine Complications
Chairpersons: Ali Taher (Lebanon) and Michael Angastiniotis (Cyprus)
09:00 – 09:20  Growth in thalassaemia patients – AT Soliman (Egypt)
09:20 – 09:40  Update in the treatment of diabetes in thalassaemia – Ratna Chatterjee (UK)
09:40 – 10:10  Fertility and pregnancy in thalassaemia – Rekha Bajoria (UK)
10:10 – 10:40 The burden of osteoporosis in thalassaemia – Ratna Chatterjee (UK)
10:40 – 11:10 Case presentation and interactive discussion – Ratna Chatterjee and Rekha Bajoria (UK) and A. T. Soliman (Egypt)

S7 – Liver Disease in Thalassaemia
Chairpersons: Ala Sharara (Lebanon) and Adlette Inati-Khoriaty (Lebanon)
11:30 – 11:50 Overview of liver disease in thalassaemia – Maria-Domenica Cappellini (Italy)
11:50 – 12:10 Treatment of hepatitis C and B virus infection in thalassaemia – Ala Sharara (Lebanon)
12:10 – 12:30 Case presentations and interactive discussion – Maria-Domenica Cappellini (Italy) and Ala Sharara (Lebanon)

S8 – Thalassaemia Intermedia
Chairpersons: John Wood (USA) and Athanasios Aissopos (Greece)
13:30 – 13:50 Pathophysiology and complications of thalassaemia intermedia – Maria-Domenica Cappellini (Italy)
13:50 – 14:10 Thrombosis in thalassaemia intermedia – Ali Taher (Lebanon)
14:10 – 14:30 Cardiac complications and their management in thalassaemia intermedia – Athanasios Aessopos (Greece)
14:30 – 14:50 Hydroxyurea in the management of thalassaemia intermedia – Mehran Karimi (Iran)
14:50 – 15:30 Case presentations and interactive discussion – Maria-Domenica Cappellini (Italy), Ali Taher (Lebanon) and Athanassios Aessopos (Greece)

S9 – Stem Cell Transplantation
Chairpersons: Abdullah Al-Jefri (Saudi Arabia) and Michele Lipucci di Paola (Italy)
16:00 – 16:30 Stem cell transplantation in thalassaemia: who is a candidate? – Abdullah Al-Jefri (Saudi Arabia)
16:30 – 16:50 BMT experience in Iran – Ardeshir Ghavamzadah (Iran)

S10 – Molecular Therapeutic Potentials
16:50 – 17:10 Gene therapy: is it a reality? – Farid Boulad (USA)
17:10 – 17:30 Fetal globin induction in β-thalassaemia – Amal El-Beshlawy (Egypt)

S11 – Reference Thalassaemia Centers
17:30 – 18:00 Requirements for a reference or expert thalassaemia centre. Copying the European efforts? – Michael Angastiniotis (TIF)
18.00 – 18.15 Conference outcome – Future Direction – Androulla Eleftheriou (Cyprus)
# 1st Pan-Middle East Conference on Haemoglobinopathies

Damascus, Syria – 2 May 2009

## Patients/Parents’ Programme

### Session 1 – Blood Transfusion & Iron Chelation

Chairpersons: Androulla Eleftheriou (TIF) and Riyad Elbard (Canada)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00 – 09:20</td>
<td>Blood Transfusion: basic requirements</td>
<td>Maria-Domenica Cappellini (Italy)</td>
</tr>
<tr>
<td>09:20 – 09:50</td>
<td>Iron overload: current protocols and new advancements</td>
<td>Paul Telfer (UK)</td>
</tr>
</tbody>
</table>

### Session 2 – Thalassaemia Intermedia & Cardiac Complications

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:50 – 10:10</td>
<td>Thalassaemia Intermedia</td>
<td>Ali Taher (Lebanon)</td>
</tr>
<tr>
<td>10:10 – 10:40</td>
<td>Cardiac complications in thalassaemia major: assessment and monitoring</td>
<td>John Wood (USA)</td>
</tr>
<tr>
<td>10:40 – 11:00</td>
<td>Cardiac complications in thalassaemia intermedia: assessment and monitoring</td>
<td>Athanasios Aissopos (Greece)</td>
</tr>
</tbody>
</table>

### Session 3 – Endocrine Complications

Chairpersons: Michael Angastiniotis (TIF) and Ramli Yunus (Malaysia)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:30 – 11:50</td>
<td>Growth in thalassaemia patients</td>
<td>AT Soliman (Egypt)</td>
</tr>
<tr>
<td>11:50 – 12:10</td>
<td>Fertility and pregnancy in thalassaemia</td>
<td>Rekha Bajoria (UK)</td>
</tr>
<tr>
<td>12:10 – 12:30</td>
<td>Osteoporosis in thalassaemia</td>
<td>Ratna Chatterjee (UK)</td>
</tr>
</tbody>
</table>

Chairpersons: Nailiya Guilyeva (Azerbaijan) and Maria-Domenica Cappellini (Italy)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:30 – 14:00</td>
<td>Treating diabetes in thalassaemia major</td>
<td>Ratna Chatterjee (UK)</td>
</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Treatment of chronic Hepatitis B and C</td>
<td>Ala Sharara (Lebanon)</td>
</tr>
</tbody>
</table>

### Session 4 – Psychosocial Support and Social Integration

Chairpersons: Mouna Haraoui (Lebanon) and Fatemeh Hashemi (Iran)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:30 – 14:50</td>
<td>Psychosocial problems – patient’s perspective</td>
<td>Anton Skafi (Palestine)</td>
</tr>
<tr>
<td>14:50 – 15:10</td>
<td>Integration into society</td>
<td>Louis Pericleous (Cyprus)</td>
</tr>
<tr>
<td>15:10 – 15:30</td>
<td>Doctor-patient relationship: build and responsibilities</td>
<td>Riyad Elbard (Canada)</td>
</tr>
</tbody>
</table>

Chairpersons: Shobha Tuli (India) and Panos Englezos (TIF)

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:00 – 16:20</td>
<td>Patients’ rights</td>
<td>Androulla Eleftheriou (TIF)</td>
</tr>
<tr>
<td>16:20 – 16:40</td>
<td>Government-patient relationship: build and responsibilities</td>
<td>Fatemeh Hashemi (Iran)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:40 – 18:00</td>
<td>Questions and answers session / Personal stories / Discussion</td>
<td></td>
</tr>
<tr>
<td>18:00</td>
<td>Closing remarks – Outcome of Conference – Future Plan of Action</td>
<td>Panos Englezos (TIF)</td>
</tr>
</tbody>
</table>
Annex 2: Conference evaluation

Conference Evaluation

Conference evaluation questionnaires were handed out at the conference to all participants. 66 valid questionnaires were returned (a response rate of 17.51%). Below is a summary of the responses. The evaluation will serve as a useful guide for the organisation of future events.

The event was attended by 237 health professionals and 140 patients/parents from 15 countries: Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Morocco, Oman, Qatar, Saudi Arabia, Syria, United Arab Emirates and Yemen.

Of the health professionals, 90% stated they attended the conference to learn about the current state of clinical management. Only 10% stated learning about prevention as the most important reason. This shows that there is a clear need for regular updating of the knowledge of health professionals on current standards of clinical management, while prevention is also an important topic.

Of the patients and parents, the majority (60%) attended in order to learn about their disease and 40% stated networking with others as their main reason for attending.

Overall, the conference was very well received by almost all of the participants and was considered very relevant and valuable to their work. The quality of the presentations was judged to be generally very good, with 92.2% of participants giving it a grade of excellent or very good and 7.8% moderate. The contents were judged as very useful by 96.5% of participants and as moderately useful by 3.5%. Almost all participants felt that the programme covered all relevant topics, with 2.5% requesting more coverage of sickle cell disease.

The format of the conference was evaluated as excellent or very good by 90.4% of the participants, moderate by 7.2% and poor by 2.4%. The latter may be explained by the wish expressed by 80.5% of the health professionals to listen to more case studies. Some 69% also suggested that discussions on particular "hot topics" in smaller groups would be very useful.

An overwhelming majority saw the conference as an important opportunity to develop networking, which is a useful guide to structuring future events so that they ensure sufficient time and opportunities for networking activities.
Annex 3: Abstracts of presentations

Session 1 – Epidemiology and Prevention in the Middle East Region

Screening programmes for haemoglobinopathies globally and in the Eastern Mediterranean Region

Dr Hussein A Gezairy, WHO Regional Director for the Eastern Mediterranean

Abstract

Regional studies have shown the prevalence of haemoglobinopathies to be relatively high in a number of countries of the WHO Eastern Mediterranean Region. In member countries of the Gulf Cooperation Council and in neighbouring countries such as the Islamic Republic of Iran, Iraq, Jordan, Lebanon, Palestine and the Syrian Arab Republic, sickle cell disorder, β-thalassaemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency are responsible for a major proportion of infant mortality and morbidity, as well as for considerable financial burden on the family and public health services.

Consanguineous marriage, which is common and culturally accepted in the region, is considered one of the main determinants of haemoglobin disorders. Low educational levels, limited budgets for preventive programmes and lack of epidemiological evidence increase the risk of having children affected with haemoglobin disorders. Despite the difficulties that exist, several countries in the region have initiated cost-effective prevention programmes for thalassaemia and sickle cell anaemia. Such programmes include carefully planned legislation on pre-marital screening and genetic counselling, newborn screening and early carrier detection.

Overview

Globally about 7% of the world’s population is a carrier of an abnormal haemoglobin gene. Each year about 300,000–400,000 infants are born with a severe form of abnormal haemoglobin disorder: thalassaemia syndrome (30%) or sickle-cell anaemia (70%).(1) Estimates of β-thalassaemia in the region (Figure 1) show that between 3% and 6% of the regional population is affected with β-thalassaemia.(2) Studies indicate that haemoglobin disorders are prevalent in Saudi Arabia. A high incidence of the major sickle cell disorders has been shown for some areas of Saudi Arabia.(3) Recent studies in Bahrain show a drop in the incidence of sickle cell diseases to 0.7% among neonates. The prevalence of sickle cell trait ranges between 12% and 13% among students.(4) The economic burden of haemoglobin disorders is well documented in some countries in the region. In Pakistan, for example, the average cost of iron chelation therapy in transfusion-dependent thalassaemic patients is US$4,400, or 10 times the average annual income. Treatment costs for one year currently amount to 4% of government health expenditure.(5)

Consanguineous marriage, which is common and culturally accepted in the region, is considered one of the main determinants of haemoglobin disorders. The predominance of large tribal groups in many countries in the region further complicates the epidemiology of genetic disorders. Low educational levels, limited budgets for preventive programmes and lack of epidemiological evidence increase the risk of having children affected with haemoglobin disorders. Preventive strategies in the region focus on early detection of carriers and effective screening and counselling to prevent the birth of an affected child. Control strategies include early interventions to prevent clinical manifestation in affected individuals and provision of adequate care and rehabilitation of affected individuals. To prevent the birth of an affected child, various screening measures have been adopted by countries of the region, including pre-marital screening, student screening, newborn screening, prenatal screening and counselling and health education. Legislation and adoption of pre-marital screening is of particular significance in the region and provides a major step towards prevention and control of haemoglobinopathies. Pre-marital screening is mandatory in most countries of the region; however, enforcement is weak in some countries.

Prenatal diagnosis and termination of pregnancy are not offered widely to carrier couples in Islamic countries, where there are religious and cultural constraints with regard to abortion of the affected fetus. The success of the Cyprus thalassaemia control programme has encouraged countries in the region to adopt the same measures.
Conclusions and recommendations

- Prevention programmes for haemoglobin disorders are feasible and cost effective.
- Carriers can be identified through population, newborn, school-based, pre-marital and prenatal screening.
- In the Eastern Mediterranean Region, many countries have adopted legislation for pre-marital screening as a key mechanism and major step towards prevention of genetic blood disorders.
- Successful implementation of prevention programmes requires awareness among professionals and the community.
- Research needs to be encouraged to generate data on the magnitude of the problem and strengthen prevention and control of haemoglobin disorders in the region.
- Preventive programmes need to be integrated into primary health care services.
- Public awareness and family education are effective preventive measures.
- Building regional and national capacity through training and education is paramount in the region.
- Enforcement of legislation on pre-marital screening and counselling needs to be promoted.
- Clinical care of affected individuals should be strengthened, and clinical and managerial guidelines on community control of genetics and haemoglobin disorders updated.
- Regional and global networks and partnerships should be developed to disseminate better practices.

![Figure 1: Estimated percentages of β-thalassaemia in selected countries of the region](image)

References

Ethical Issues on Prevention and Management – Islamic point of views
Mohsen AF El-Hazmi, BSc, MB, BChir, PhD (Cantab), FRCPath (UK)
Director, WHO Collaborating Center for Genetic Disorders, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Ethical issues are of concern to all members of the health team and the community at large, particularly in relation to chronic and genetic diseases. The fear from the negative social impact, including stigmatization of the carriers of a genetic disease and the affected individual is of a particular concern to the individual and his family. Members of the health team should protect the individual autonomy and observe the ethical principles including beneficence, non-maleficence, justice, confidentiality and maintain high level of professional competence.

Both prevention and management of blood genetic disorders require observing ethical principles and prevailing tradition in the concerned communities. Islamic/Arab costumes and traditional need to be respected in these communities. In addition, there are unique features as well as religious teachings that colour the life patterns. This paper will outline prevention and management methods and approaches to common blood genetic disorders in the high of Islamic ethical teachings, where the individuals benefit is paramount.

Preimplantation Genetic Diagnosis
Dr Mary Petrou, Haemoglobinopathy Genetics Centre, University College Hospitals NHS Foundation Trust and University College London, UK

Couples at risk for having an affected child with homozygous thalassaemia or other serious haemoglobin disorder have various options in prevention. The most used in some countries has been prenatal diagnosis with a choice of termination of pregnancy. A more recent addition is pre-implantation genetic diagnosis (PGD). In this article this method is described and reviewed.

Introduction
Haemoglobin disorders constitute the most common lethal inherited disorders worldwide. They are common in populations in tropical Africa, Asia and the Mediterranean region and have spread by migration throughout the world. It is estimated that 307,900 children are born annually with a severe haemoglobin disorder and 60-70% of births occur in sub-Saharan Africa. Consequently, sickle cell disease (SCD) accounts for 70% of haemoglobin disorders worldwide because of the high frequency of the gene. In Africa it is estimated that 224,200 infants are born annually with a sickle cell disorder and most die before they reach the age of five. Thalassaemia is prevalent in the Mediterranean area, the Middle East, South East Asia and the Pacific. The carrier rates range from 2% to 19% in the different populations. The birth prevalence of the haemoglobin disorders in countries affected by migration of populations varies according to the geographic location and the origin of the populations.

Couples who are at risk for producing children with a major haemoglobin disorder such as β-thalassaemia major or a sickle cell disorder have the option of avoiding the birth of an affected child with prenatal diagnosis. Although prenatal diagnosis is widely available globally, there are several countries where it is not available to the at-risk population. Despite prevention programmes, only a tiny fraction of affected births are prevented by prenatal diagnosis.

Even when PND is available, there are couples for whom prenatal diagnosis is not an option as prenatal diagnosis and selective abortion of an affected fetus is unacceptable to them for moral or religious objections to termination of pregnancy of an affected child, or their own personal reasons. Termination of pregnancy of a wanted child is often a traumatic decision, particularly when the pregnancy is advanced. Many couples who undergo repeated termination of pregnancies in an attempt to have a healthy family, feel they cannot cope with further terminations. For such couples, PGD is the only option.
Pre-implantation genetic diagnosis (PGD)
PGD involves the diagnosis of a genetic disorder in embryos obtained through IVF, selection of healthy embryos and transferring them to the mother’s uterus. The first application of PGD was in 1988, by Handyside et al. at the Hammersmith IVF unit in London, who reported that the biopsy of up to two cells from the eight-cell stage embryo did not affect the development of the embryo to the blastocyst stage, or the embryo metabolism (1). The PGD case was for sex determination for couples carrying an X-linked disorder. The polymerase chain reaction (PCR) was the first single-cell diagnostic method to be used to amplify a Y-chromosome repeat sequence (2). The Chicago PGD group in the same year used PGD for sex selection using polar body biopsy (PB) (3).

Since then, the centres performing PGD have increased along with the number of diseases that can be tested. To date it is estimated that PGD for single cell disorders has been performed in more than 50 different centres in more than 3,000 cycles (4, 5). PGD has become an important technique to couples at risk for β-thalassaemia (6) and sickle cell anaemia (7). The ESHRE 2006 data reports 279 cycles performed for the haemoglobin disorders (including for HLA); however, this data omits the three largest PGD centres (5). PGD is possible for a large number of monogenic disorders. The most frequently diagnosed autosomal recessive disorders are cystic fibrosis, β-thalassaemia, sickle cell disease and spinal muscular atrophy. PGD has been used not only to avoid the risk of having an affected child, but also for preimplantation HLA antigen matching for pre-selection of potential donor progeny for an affected sibling who requires bone marrow transplantation (8). At our centre we have seen this as an increasing request from couples at risk for β-thalassaemia who have an existing affected child.

Organisation of a PGD centre
To be successful, it requires close collaboration between the assisted conception centre and the genetic teams. Before an IVF unit embarks on a PGD programme they should ensure they have good IVF success with a good pregnancy rate. Staff training is essential; embryologists should perform the biopsy, the PCR should be performed by a trained molecular geneticist/biologist. For an optimal PGD centre the requirements are communication, an excellent IVF programme, excellent genetic diagnostic centre, integration of services, rigorous quality control, follow up of PGD couples and babies.

PGD and IVF consultation
Evaluation of the patient is essential and specific PGD counselling should be provided explaining the pros and cons of PGD and the other reproductive options available to the couple. The couples need to be given time to consider their options and the right choice for them. PGD patients are also evaluated by the IVF team. Briefly, the pre-treatment work-up usually includes an infection screen, assessment of uterine cavity (Hycoy), dummy embryo transfer, genetic screen for severe male factor infertility and assessment of ovarian reserve (OST). Stimulation is dependent on the ovarian reserve. Down regulation is achieved using gonadotrophin-releasing hormone (GnRH) followed by ovarian stimulation with FSH. Transvaginal oocytes retrieval is scheduled 34-38 hours after the administration of human chorionic gonadotrophin. The success of IVF and PGD is very much dependent on the number of eggs available.

IVF and PGD
For all single gene disorders, intracytoplasmic sperm injection (ICSI) is performed in order to reduce the risk of contamination by sperm DNA. A single sperm is injected directly into the cytoplasm of the egg, and fertilization is assessed 18 hours later. There are two phases to the PGD; first the removal of cells from the oocyte or embryo and secondly the diagnosis.

Embryo biopsy
Cell biopsy involves two steps: the puncture of the zona pellucida surrounding the oocyte or embryo, and the removal of a cell or cells. This can be achieved by polar body biopsy, cleavage stage biopsy, or blastocyst biopsy.

Polar Body Biopsy: The polar body ideally should be removed within 6 hours of oocyte retrieval; the second PB is removed from the zygote. However, in practice both polar bodies may be biopsied together from the zygote (3).

Cleavage Stage Biopsy: The human zygote undergoes mitotic division every 24 hours before compacting to form the morula on day 4. On day 3 when the embryo is at 6-8 cell stage, two blastomeres can be

41
removed without affecting the embryo metabolism or development (1) and more than 90% of embryos survive the procedure with a successful biopsy achieved in 97% of cases (4). Embryo biopsy requires zona drilling and blastomere aspiration using a micromanipulator. The limitation of cleavage stage biopsy is that only 1-2 cells can be removed, and that time is limited to 24 hours to complete the analysis in order to transfer the embryo on day 4.

Blastocyst biopsy: can be performed on day 5 or 6 post insemination (9), 10-30 trophectoderm cells can be removed without harming the inner cell mass. The problems associated with single cell PCR such as allele drop out or amplification failure virtually disappears, as 10-20 cells are available for testing.

Genetic diagnosis of single gene disorders
In PGD, PCR is a powerful molecular technique for amplifying a particular DNA fragment to a stage that can be analysed and detected. However, it is still challenging to obtain a reliable diagnosis on a single cell where amplification failure (AF), allele dropout (ADO), and extraneous DNA contamination are still major problems. Some misdiagnoses have been reported by the ESHRE consortium (10) and a number of other groups, and these have been mainly caused by the phenomena of ADO and contamination.

Molecular strategies to overcome problems associated with single cell PCR
Different molecular strategies have been incorporated in PGD to help prevent misdiagnosis. This includes nested PCR, multiplex PCR, Fluorescent PCR, and the use of microsatellites and other polymorphic markers. The sensitivity of PCR based protocols have been increased 1,000-fold compared to conventional non-radioactive methods by the use of fluorescent PCR and the detection of the PCR products on a fluorescent DNA sequencer. Several loci can be investigated in one reaction in a multiplex reaction if the primers are labelled with different fluorescent dyes (11, 12).

Nested PCR enhances the specificity of amplification, as well as reducing the risk of carry over contamination. It requires two serial amplification reactions. The first PCR amplifies the sample template, using an external set of primers to produce a DNA fragment encompassing the entire mutation site. This then becomes the template for the second round of PCR amplification, which uses specific internal primers, situated within the first external primers (nested PCR), or by using one of the previous external primers with one internal primer (hemi-nested PCR). This should amplify sufficient product for visualisation and further analysis.

DNA analysis for haemoglobin disorders
Different molecular approaches at the single cell level have been used for single gene defects. Scanning methods are used to detect mutations in a population with a large number of β-thalassaemia mutations. Methods used for PGD include, denaturing gradient gel electrophoresis (DGGE) (13), mini sequencing (14), site specific mutagenesis and restriction enzyme PCR, (6,12), reverse dot blot (15), polymorphic linked markers (6), multiple displacement amplification (MDA) (16).

PGD for haemoglobin disorders combined with HLA matching is also an increasing indication for PGD; the HLA genes are tested using microsatellites in the HLA region using a nested multiplex or heminested PCR system involving only closely linked polymorphic short tandem repeat markers located along the HLA region (17,18).

In conclusion, PGD was first reported 21 years ago, but still remains a stressful, intensive and relatively expensive process. It is an effective tool for genetic screening and from the patients’ perspective PGD can be used instead of PND to avoid the birth of affected children. However, the low pregnancy and birth rates and the high cost of the procedure make it unlikely that PGD will supersede prenatal testing. PGD is a complex combination of different technologies. Further advances in molecular genetics and assisted reproductive technologies will likely increase the use of PGD in the future.

References


Prevention of Haemoglobinopathies in Syria

Kusai Al Zir, MD, Professor of Medicine – Pediatrics & Haematology, Head Of Thalassaemia Patient’s Friends Association And Hereditary Blood Diseases, Syria

Syrians – as the rest of the Mediterranean countries peoples – have the haemoglobinopathies genes in different degrees in cities and at average of 5–7% of the total population, and this degree increases annually in steady state.

The total number of patients in 2008: 7,785
The total of NEW patients in 2008: 786

And for the geographic distribution of the haemoglobinopathies disorders, taking in consideration that Damascus City is considered to have the highest population in Syria:
Damascus 33.3%; Aleppo 18.4%; Hama 8%; Homs 5.6%; Idleb 6.5%; Daraa 5.5%; Latakia 5.7%; Tartous 4.9%; Raqqa 3.7%; Qamishli 2.5%; Dier Al Zour 3.5%.

We can find that the percentage varies according to the type of haemoglobinopathies disorder, and it is higher in the middle, coastal and southern areas than the eastern area. Those patients are treated and clinically followed up at city centres, and there are better services as blood transfusion to iron chelation, as a new therapy plans have been put while the classical medication is still the Desferal and the pump. By adding the oral chelation such as Deferiprone, and it is used for patients with iron overload and age over 10 years. Deferasirox is used for patients with ages less than 10 years. And due to the high cost of the iron oral chelation, the government and according to a studied plan will increase the iron oral chelation up by 10–20 % annually to relieve the patients from the pump.

The annual increase of patients and enormous cost of the treatment and complication medication cost put a high pressure on both government and society, which lead us to adopt new prevention plans as:

- Establishing clinical centres for the pre-marriage test in all cities, in cooperation with the Syrian medical syndicate, and trying to avoid carriers from marriage.
- Increase public awareness by using the means of media
- Using the schools to educate the students and increase the knowledge of the military personnel.
- Lecturing in universities, seminars and civic centres.
- Increase awareness through mosque and churches preaches
- Working to do a full scale screening to categorize the high-risk families.
- Trying to adopt new laws to prevent carriers from marriage.
- Improve the life of the patients and decrease complications
- Monitoring patients closely and provide better medical services.
- Using the experience of the neighbouring countries and Mediterranean countries and applying the methods which fit our society.

Prevention of Haemoglobinopathies In Egypt

Amal El Beshlawy, Professor of Pediatric Hematology, Cairo University; President of the Egyptian Thalassemia Association (ETA)

Egypt, the oldest civilization in the Mediterranean region and the whole world, has a population number of 72,010,572. β-thalassaemia is the most common hereditary chronic haemolytic anaemia in the country. The first case was described in 1944 in the paediatric hospital of Cairo University. The carrier rate varies between 5.3 to > 9% in studies which have been done in 5,000 candidates in different governorates of Egypt from 1993 to 2005. (1) The gene frequency is 0.03, it was estimated that 1,000/1.5 million/year live births born with thalassaemia disease (total live births 1,936,205 in 2006). (2) The registered cases of thalassaemia in the big centres are approximately 9,912 and for sickle/β-thalassaemia (S/β-thal) 757 with the highest numbers in the paediatric hospital of Cairo University (2,597 and 194 respectively).

Number of thalassaemia patients in the Pediatric Hematology Clinic, Cairo University from 1982 to 2008:
Prevention of thalassaemia

There is no national prevention program for thalassaemia in Egypt though it is highly needed.

Objectives for the need of a prevention program in Egypt:
- High frequency of β-thalassaemia carriers
- High rate of newly born cases
- β-thalassaemia creates a need for life long regular blood transfusion and chelation
- β-thalassaemia creates a social and financial burden for the patient, family and government. The average estimated financial burden for thalassaemia management in Egypt is 10 million USD/year.

Session 3 – Iron Chelation Therapy

Iron overload: consequences, assessment and monitoring

Ali Taher, MD, Professor of Medicine, Hematology-Oncology Division, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Abstract

In patients suffering from transfusion-dependent anaemias in general and thalassaemias in particular, excess iron associated with regular repetitive transfusions cannot be physiologically excreted, thus leading to chronic iron overload with iron accumulating in the liver, heart, and other endocrine organs and ultimately resulting in a range of clinical problems including diabetes, hepatic and cardiac dysfunctions and eventually premature death. Historically, iron overload was assessed through measurement of serum ferritin or direct determination of liver iron concentration by means of biopsy. Although both correlate well with iron overload severity, several limitations pertinent to both are of concern. This has led to the identification of novel non-invasive iron assessment techniques, namely magnetic resonance imaging R2 and T2*. Moreover, investigation of other serum parameters like non-transferrin bound iron (NTBI) and labile plasma iron (LPI) has also shown promising results. Optimal iron overload assessment and monitoring is a key element in the development of improved strategies of iron chelation therapy which can be tailored to meet the patient's specific needs.

Overview

Iron is a transition metal which is essential for the functioning of proteins involved in oxidative energy production, oxygen transport, mitochondrial respiration, inactivation of harmful oxygen radicals and DNA synthesis. Because of its poor solubility, living organisms have developed efficient mechanisms for the uptake, transport and storage of iron. In a non-disease state physiological iron homeostasis results in exchange of only 1–2mg per day of iron between the body and the environment. When this homeostasis is disrupted the body quickly becomes overloaded with iron. In thalassaemia, myelodysplastic syndrome (MDS) and sickle cell disease (SCD), long-term substitution therapy for anemia results in toxic iron overload, which constitutes a significant medical problem. The subtle balance of normal iron homeostasis
is grossly overwhelmed by the abnormal erythropoiesis associated with thalassaemia major, sickle cell
disease, and myelodysplastic syndrome. As a result of ineffective erythropoiesis, plasma iron turnover
increases 10 to 15-fold, resulting in a relative failure of hepcidin production and an outpouring of catabolic
iron, which exceeds the iron-carrying capacity of transferring.(1) This leads to the emergence of toxic non-
transferrin-bound iron (NTBI), which is directly involved in the production of harmful oxygen derivatives
and damage to vital tissues.(2) This is exacerbated by the treatment of the patient's anemia by blood
transfusion, which again adds excess iron into the body. The net state that results is one of iron overload.
The level of iron overload is generally proportional to the number of transfused units and is cumulative.(3)

Consequences of iron overload
As iron overload may progress unnoticet over many years, patients are often severely affected by the
time they develop symptoms. Uncontrolled iron overload has serious clinical consequences resulting in
significant morbidity and mortality. Frequent manifestations include liver damage, cardiac disease and
endocrine dysfunction. Iron overload can also result in arthropathy, neurodegenerative disorders,
hyperpigmentation, pulmonary hypertension and carcinogenesis. The liver is the primary site of iron
storage. Liver damage develops in parenchymal cells leading to mild to moderate hepatomegaly followed
by fibrotic and cirrhotic shrinkage. Portal fibrosis often occurs within two years of starting blood
transfusions, and liver cirrhosis can develop within a decade unless the iron overload is treated.(4)

The loading of iron in the heart is slower than in the liver, and cardiac dysfunction related to iron overload
usually appears after years of exposure. Cardiac disease caused by transfusional iron overload remains
the principal cause of death in patients with thalassaemia major despite improvements in iron chelation
therapy over the past 25 years. This is most likely due to poor compliance to chelation therapy. The
severity of cardiac disease depends on the amount of iron deposited in individual myocardial fibers and
the numbers of fibers affected. Persistently increased intracellular labile iron in cardiac tissue diminishes
the contractility of cardiomyocytes and can lead to myocarditis, pericarditis, and atrial/ventricular
arrhythmias. The degree of cardiac iron overload is cumulative and generally proportional to the number
of transfused units.(4)

In clinical practice, liver and cardiac iron burden may not correlate in a cross-sectional analysis, which
may be due to medical history, particularly previous use of chelator. Importantly, even without a high
heart damage is poor, as cardiac failure often develops rapidly. However, reduced ventricular function is
measurable long before the development symptomatic heart disease, allowing the initiation of appropriate
therapy. Prospective data confirm that siderotic heart failure is often reversible by iron chelation.
Reductions in serum ferritin can predict reduced cardiac risk and are associated with improved disease-
free survival in patients with thalassaemia major.(4)

Endocrine dysfunction is common in thalassaemia patients with iron overload and is also found in patients
with sickle cell disease. Patients younger than 10 years of age often experience growth failure; diabetes
mellitus can develop when iron deposition in the interstitial pancreatic cells affects microcirculation,
leading to insulin deficiency. Pituitary dysfunction results in a plethora of conditions, including
hypogonadism, which is common in thalassemia patients with iron overload and reduced parathyroid
activity.(4)

Assessment and monitoring
The first step in patient management is to define how much iron excess iron is present within the body.
Then decisions can be made on what is the therapeutic goal for that patient, i.e. must excess stored iron
be removed? or is there sufficiently low iron stores that iron balance must be maintained to match iron
intake? Historically two methods have been used to assess iron burden, namely monitoring of serum
ferritin and liver iron concentration (LIC) via biopsy. Both serum ferritin and liver biopsy have advantages
and disadvantages. Serum ferritin monitoring has been the method of choice within the clinic as it is easy
to assess, inexpensive, provides repeat serial measures that are useful for monitoring chelation therapy,
and it has positive correlation with morbidity and mortality allowing longitudinal follow-up of patients.(5)
However, several limitations exist concerning the use of serum ferritin: it represents indirect measurement
of iron burden; fluctuates in response to inflammation, abnormal liver function, ascorbate deficiencies;
appears to underestimate the extent of iron overload in thalassaemia intermedia and sickle cell disease.
patients; and may not reflect organ specific iron overload.(6) Liver biopsy, on the other hand, provides a direct measurement of LIC, being quantitative, specific and sensitive, and has also been shown to be positively correlated with morbidity and mortality. However, the technique is invasive and can be painful, carrying a risk of potentially serious complications such as bleeding. In addition, there is a significant risk of sampling error and there is currently poor standardization between laboratories. Thus, it is conceivable that a non-invasive technique such as MRI may allow regular monitoring of LIC to become standard medical practice. In addition, multiple convenient LIC measurements may be beneficial in chelator dose titrations or assessing the need for dose adjustments in a patient.

These non-invasive methods are based on the magnetic properties of iron molecules, which influence their immediate environment. This disturbance can be detected by magnetic resonance imaging (MRI), resulting in a quantifiable signal. Of the methods available there are two which are currently becoming more widely available, namely R2-MRI(7) and T2*MRI.(8) The former of these, R2-MRI, has been validated and recently received marketing approval from a number of regulatory authorities, including the FDA. It is becoming increasingly available worldwide. Among its limitations are: the indirect measurement of LIC; requirement of an MRI imager with dedicated imaging method; and children under the age of 7 years requiring a general anaesthetic. Cardiac T2* is still an experimental method, but has been used in a number of clinical studies and part of standard medical practice in some centres. Both imaging techniques are becoming highly sought methods for monitoring iron chelation therapy.

In addition to these non-invasive methods of monitoring iron, interest has generated in the monitoring of non-transferrin bound iron (NTBI), which correlates well with LIC. NTBI is the free iron that mediates tissue damage by stimulating free radical formation and lipid peroxidation in cell membranes, thus it is of clinical relevance to get new insights about its kinetic in order to establish the effectiveness of chelation therapy in removing this form of toxic iron. Recent studies have shown that NTBI encompasses forms of iron that are readily chelated.(9) This fraction referred to as labile plasma iron (LPI), the pathologically relevant one, includes cell-penetrating forms of iron that are redox active and susceptible to chelation. Recently Cabantchik et al.10 showed that in thalassaemia patients on overnight deferoxamine (DFO) infusion, LPI was essentially undetectable during the course of DFO infusion, returning on cessation of therapy and peaking at evening hours just before the next infusion.

Conclusion
Close monitoring of iron accumulation and subsequent chelation therapy is crucial to control iron burden or avoid over chelation, respectively. Improved, more convenient monitoring techniques for iron burden together with a better understanding of the pathophysiology of iron toxicity and the mechanism of iron chelation is expected to lead to the development of improved strategies of iron chelation therapy which can be tailored to meet the patient's specific needs.

References


Iron Chelation: treatment with Desferrioxamine and Deferiprone
MD Cappellini, E.Cassinerio, A.Maronc,L.Zanaboni, Policlinico Foundation IRCCS-University of Milan-Milano, Italy

Abstract
Desferrioxamine (DFO) is the reference-standard iron chelator whose safety and efficacy profile has been established through many years of clinical use. DFO side effects are acceptable and manageable however the prolonged subcutaneous infusion regimen of 5-7 days per week is very demanding and results in poor adherence to therapy. Deferiprone (Ferriprox, L1) is a bidentate molecule, orally administrable three-times/day, licensed in Europe and in other regions but in the USA and Canada, for the treatment of iron overload in patients for whom DFO therapy is contraindicated or inadequate. Preliminary evidences suggest that Deferiprone may be more effective than DFO in chelating cardiac iron. The side effects include gastrointestinal symptoms, liver dysfunction, joint pain, neutropenia and agranulocytosis. A weekly assessment of white blood cell counts is recommended because of the risk of agranulocytosis.

Desferrioxamine
Desferrioxamine (Desferal ) was discovered in 1960 (Ciba) and it was introduced in 1963. Desferrioxamine has been in clinical use since the 1970s and widely used as subcutaneous infusion since about 1980. Due to its molecular size, it is poorly absorbed from the gut. Desferrioxamine has a short plasma half-life (initial half-life 0.3h), being eliminated rapidly in urine and bile. The process of iron chelation ceases soon after an infusion of desferrioxamine is completed. The efficiency of desferrioxamine (measured in terms of percent of dose excreted in the iron bound form) administered by subcutaneous infusion at standard 8–12 hour intervals 5–7 days a week is approximately 14%. Providing that the treatment was started within 2–3 years of beginning transfusion therapy, regularly administered in adequate doses, Desferrioxamine had a well established impact on survival and on cardiac and other complications of iron overload. Symptomatic heart disease can be reversed by high dose intravenous treatment. Continuous intravenous doses of 50–60mg/kg/day typically normalised left ventricular ejection fraction (LVEF) in a period of three months, significantly before liver or heart iron stores had been normalised. However, if advanced heart failure has developed before treatment is intensified, the chances of successful rescue are decreased. Recent data show that a significant portion of patients on long term s.c. DFO with good compliance and low serum ferritin levels has evidence of cardiac iron loading. Local skin reactions, such as itching, erythema, and mild to moderate discomfort are common during DFO treatment. Skeletal changes in children have been reported in cases of excessive dosage of desferrioxamine or where patients have a low level of iron loading. Rickets-like bony lesions, genu valgum and vertebrae flattening where seen as long term results of overchelation from DFO high doses in patients with low iron load. disturbances of hearing and vision have been reported including retinal and lenticular abnormalities. Ophthalmological and audiological tests should be therefore carried out before starting treatment with Desferrioxamine as well as yearly during treatment. Infection with Yersinia enterocolitica is an important risk associated with desferrioxamine treatment. Although Desferrioxamine during the last 30 years has changed the outcome of morbidity and mortality for thalassaemia, the poor patients adherence to the effective standard treatment and the non availability in several countries because of costs remain two major concerns that significantly limited the beneficial effects of iron chelation.

Deferiprone
Deferiprone (Apotex, Toronto, ON, Canada) also known as L1, CP20, Ferriprox and Kelfer was synthesized and tested as iron chelator at the University of Essex in the early 1980s. Deferiprone is a bidentate molecule that forms 1:3 iron-chelator complexes. It is rapidly absorbed and the mean half-life was reported 160 and 91 minutes respectively in two different studies. The first use of Deferiprone in
Humans, was reported in 1987 from the Royal Free Hospital in London in three iron-overloaded patients with myelodysplesia and subsequently in TM patients. Over the next 20 years many patients with thalassaemia and other haemoglobinopathies have been treated with Deferiprone for different periods up to 5 years or more. At present Deferiprone is licensed and currently available in the European Union and in a number of countries outside the USA and Canada for the second-line treatment of iron overload in patients with thalassaemia major for whom DFO therapy is contraindicated or inadequate (EMEA). The results of the main studies have been summarized by Hoffbrand et al appears that serum ferritin levels in TM patients plateau around 2,000–2,500ug/l (range 1779-3273) in nine published series. It seems that Deferiprone at standard dose of 75mg/kg/day is similar to DFO at removing iron from the liver although great individual variations have been observed. Deferiprone by virtue of his membrane crossing ability has been shown to shuttle tissue iron into circulation and studies in iron-loaded rat heart cells and in gerbils had shown his ability to remove iron from myocardial cells at concentrations that can be achieved in the circulation. A randomized control trial designed to estimate the changes of myocardial siderosis (myocardial T2*) over 1 year of treatment with DFO or with Deferiprone was performed by Pennell et al. in patients previously maintained on subcutaneous DFO. The dose of Deferiprone was higher (92mg/kg/day) than the standard one (75mg/kg/day). The improvement of myocardial T2* was significantly greater for Deferiprone than DFO (27% vs 13%, P=.023) whereas the changes in liver iron concentrations and serum ferritin levels were not significantly different between the two groups. Several subsequent studies strongly suggest that Deferiprone, probably because of its lower molecular weight and greater intracellular penetration is more effective at removing iron from the hearth than DFO. Wonke et al in 1998 reported on 5 TM patients safely treated over several months with Deferiprone and DFO given on the same day. The efficacy was based on increased urinary iron excretion. Since than data from several cohorts of patients treated with Deferiprone and DFO in combination have been reported. Recently, a randomized placebo controlled double blind trial showed that combined treatment is superior to DFO alone at removing myocardial iron in TM patients and improving cardiac and endothelial function. Gastrointestinal symptoms (GI) including nausea, abdominal pain and vomiting are the most common and in general occur in the first year of treatment. Arthropathy and/or arthralgia are quite common side effects particularly frequent in patients from India. The most serious side effects reported during treatment with Deferiprone are neutropenia and agranulocytosis.

Conclusions

For more than 30 years Desferrioxamine was the only iron chelator available and although it was shown to reduce the risk of developing co-morbidities due to iron overload and improve patients survival, the prolonged subcutaneous infusion regimen of 5–7 days per week resulted long term in poor adherence to therapy. Deferiprone an oral iron chelator probably because of its lower molecular weight and greater intracellular penetration seems to be more effective at removing iron from the hearth than DFO.

Suggested reading

Update on survival in thalassaemia major
Paul Telfer, MD, Consultant in Paediatric Haematology, St Bartholomew’s and The Royal London NHS Trust. Senior Lecturer in Haematology, Queen Mary, University of London

Trends in survival
Improvement in life expectancy in thalassaemia major (TM) reflects the evolution in therapy.

1. No regular transfusion: Life expectancy <5 years
2. Regular transfusion (maybe of sub-optimal intensity) and no chelation: Life expectancy 10–15 years
3. Regular transfusions and desferrioxamine (DFO) chelation: Life expectancy depends on adherence to therapy. Poor adherence, 15–25 years; Good adherence, probably at least 50 years
4. Availability of chelation options: DFO; Deferiprone (DFP); Deferasirox (DFX); Combination DFO and DFP: Life expectancy unknown, but probably in excess of 50 years.

The timing of these therapeutic milestones is well documented in several high income countries, where regular transfusion became standard therapy in the late 1960s and early 1970s, and DFO chelation in the late 1970s [1, 2, 3]. DFP was licensed in the EU in 1999, and DFX in 2006. For middle income countries, most patients have only been able to benefit from regular transfusion and chelation after economic developments in the 1980s and 1990s. Patients born in these countries before 1980 may now have good life expectancy if negative iron balance and removal of myocardial iron can be achieved. The situation remains desperate in low income countries, where transfusion and chelation is only available to those who can afford it. There are wider political, social and economical issues which need to be solved before health authorities are likely to focus on the problems of children and families struggling with a long-term genetic condition. Nevertheless, more can be done within the thalassaemia community to address this north-south differential in outcomes.

Factors associated with improved survival
Iron-induced cardiac disease is the most important, but not the only cause of early mortality in TM [1, 2, 3]. Improved survival has been associated with parameters of effective iron chelation, availability of oral iron chelators, better adherence to therapy and younger age at starting therapy (Table). Female sex seems to be protective, particularly in older cohorts, but less so with the advent of new chelation regimes [4]. This may be because females tend to adhere better to chelation therapy. Alternatively, this may reflect a general tendency for increased longevity, perhaps because oestrogens protect from cardiovascular disease.

<table>
<thead>
<tr>
<th>Protective Factor</th>
<th>Location and study population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of diabetes, heart failure</td>
<td>Multicentre, Italy</td>
<td>Borgna-Pignatti et al, 2004[2]</td>
</tr>
<tr>
<td>Switching heavily iron loaded patients from DFO to DFP</td>
<td>Multicentre, Italy</td>
<td>Borgna-Pignatti et al, 2006[9]</td>
</tr>
<tr>
<td>Switching heavily iron loaded patients from DFO to combination DFO and DFP</td>
<td>National registry, Cyprus</td>
<td>Telfer et al, 2008[4]</td>
</tr>
</tbody>
</table>
Outcomes with DFO
The main reason for the improved survival with successive birth cohorts is the availability of DFO for chelation at an early age. However, outcomes depend on transfusion load, DFO dosing and adherence. In one study, patients were 12.6 times more likely to survive for every increase of one unit in the natural logarithm of the ratio of transfusion iron load to DFO usage [6]. Even when best practice is implemented within a comprehensive care clinic, with options of different infusion devices and long-term psychological support, there is a residual group of patients who are unable to adhere, and die at an early age as a result of cardiac iron overload.

Outcomes with DFP and combination therapy
Analysis of retrospective data from well-followed cohorts show a 10 fold improvement in cardiac outcomes in severely iron overloaded patients switched from DFO to DFP [9], and a 7-fold improvement in survival in patients switched from DFO to combination therapy with DFO and DFP[4]. This is likely to be due to improved removal of myocardial iron and left ventricular function with DFP compared to DFO, though improved adherence with oral compared to sub.cut. therapy may also play a role.

Outcomes with Deferasirox (DFX)
Long-term follow-up studies of DFX trial patients are not yet sufficiently mature to confirm a favourable effect comparable with the other chelators. DFX at relatively high doses (30–40mg/kg) appears to improve myocardial iron loading over one year in patients with cardiac loading (T2*<20msec), but the improvement may be slower than with DFO/DFP combination, and is not consistently associated with increase in Left ventricular ejection fraction (Pennell D et al., Wood J et al., ASH Abstracts 2008).

Other causes of mortality
Several cases of malignancy in young patients were noted in natural history studies [2, 3, 10] with various tumours observed, including lymphoma, breast and bowel carcinoma. It is unclear whether there is a true increase in risk of malignancy, and there is a need for epidemiological studies on large thalassaemic populations to address this issue. Hepatocellular carcinoma might be considered separately within the spectrum of thalassaemic liver disease. The incidence of hepatoma appears to be increasing in Italian thalassaemics (Borgna-Pignatti, personal communication 2009), This is not surprising given the high prevalence of chronic viral liver disease in this population, and the known association between chronic viral hepatitis and iron overload with HCC. Severe acute infection remains a significant cause of early mortality. There is a constant risk of overwhelming infection from encapsulated bacteria in splenectomised patients, and from certain gram negative organisms whose propagation is facilitated by iron overload and DFO therapy, such as yersinia and klebsiella. Neutropenic sepsis is a potentially life threatening complication for the approximately 1–2% of DFP-treated patients who develop agranulocytosis.

Conclusions
Life expectancy for a patient newly diagnosed with TM in a high or middle income country is probably in excess of 50 years. DFO has greatly improved life-expectancy, but is difficult and impractical therapy. There is now substantial evidence that DFP improves survival in heavily iron loaded patients previously treated with DFO, and should be offered to all such patients, probably in combination with DFO. It is expected that long-term maintenance of safe iron levels and control of labile plasma iron in patients commenced on DFX at an early age will prevent morbidity and mortality, and one can predict that iron overload will cease to be the predominant cause of mortality for young thalassaemics. A high level of awareness of other causes of mortality should be maintained, particularly with regard to prompt treatment of infection, and consideration of anti-viral therapy to eradicate Hepatitis C virus infection where present.

References
4. PT Telfer FW, S Christou, M Hadjigavriel, M Sitarou, A Kolnagou, M Angastiniotis. Improved survival in thalassaemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. 11th International Conference on Thalassaemia and Haemoglobinopathies. Singapore; 2008.

Session 4 – Cardiac Complications

Assessment and treatment of cardiac iron overload
A Aessopos, First department of Medicine, University of Athens, ‘Laiko’ Hospital, Goudi, Athens, Greece

Abstract
Cardiac disease remains the major cause of death in thalassaemia major and iron overload is involved in heart failure development. Iron load is assessed by different means, among which cardiac magnetic resonance (CMR) measurements remain the best method for estimation. In cases of heart iron overload, chelation treatment should be appropriately tailored in terms of intensification.

Introduction
In beta thalassaemia major transfusions and iron chelation therapy have significantly improved the survival and reduced the morbidity (1). However, heart complications still represent significant morbidity and remain the leading cause of mortality in transfusion dependent thalassaemia (TM) patients (1). Cardiac structure and function in TM are mainly affected by two competing factors: iron load and increased cardiac output (CO). The cardiac iron deposition results in a decrease of left ventricular function, while the anaemia together with marrow expansion leads to volume overload and increased CO that then demands increased contractility adding additional stress to the heart (2). Knowledge derived by recent magnetic resonance imaging (MRI) studies assessing cardiac function, showed that all patients with reduced LV function had cardiac iron overload and in many cases this was severe (3). Iron overload results principally from the regular blood transfusions. In addition to the transfused iron, TM patients absorb more iron than normal individuals. The mechanism of increased absorption is thought to be related to paradoxical Hepcidin suppression from the dyserythropoiesis (4) and to the L-type Ca2+ channels which are high-capacity pathways for ferrous iron (Fe2+) uptake into cardiomyocytes in conditions of iron overload. In myocytes, iron is stored in the form of ferritin, haemosiderin and free iron, referred as the labile cellular iron (LCI). There is a significant flux between the three forms, with haemosiderin being the least accessible. The LCI is thought to be the most accessible to chelation, but it is also the most toxic form stimulating the formation of free radicals and resulting in peroxidative damage of membrane lipids and proteins provoking cellular injury, leading to impaired function of the mitochondrial respiratory chain which is clinically manifested by reduction of cardiac muscular contractility and CCF development. The potential reversibility of heart injury by iron overload removal promises an outcome better than that seen with other causes of cardiomyopathy with equivalent clinical severity in the general population. Today the great challenge in TM patients is to achieve even better results in preventing heart injury and assessment of iron load state is critical for the prevention and treatment of heart injury.
Ferritin levels
The traditional biochemical parameter, serum ferritin, was relied on universally, having an increasing linear relationship to the number of transfusions that patients received. Ferritin levels seen in iron load states mainly represent a component that has leaked out of cells. Under chelation therapy, ferritin levels most often showed significant reduction. Analysed as single measurements or as mean measurements, they had been regarded as reasonable indicators of iron load and prognosis. There have been a number of studies that relate the risk of death from cardiac disease to ferritin levels that have been maintained by patients. In a recent Italian study, deaths in TM were related to high ferritin levels at the time of death (1). Overall, persistently high levels of ferritin are associated with poor outcomes and efforts should be consistently made to maintain them low. However cardiac deaths still occurred in patients with satisfactory ferritin levels and recent studies showed disproportion and no predictive value between MRI values and ferritin levels. The limitations of ferritin levels in predicting and assessment of iron load include that it is an acute phase reactant and is reduced in the presence of low ascorbic acid (common in TM patients) (5). Furthermore, it has been shown that high levels of ferritin may be present even before the tissue iron storage is excessive and in contrast, intensified chelation therapy in heavily iron loaded patients, may rapidly reduce serum ferritin while tissue iron, especially in the heart, remains elevated (6).

Liver iron concentrations
Liver iron concentrations (LIC) were subsequently regarded as the gold standard for determining the total body iron load and as a better indicator of risks than ferritin. However, recent studies have shown that LIC (by biopsy) was not related to cardiac dysfunction misleading. Caution should be exercised, particularly in patients with satisfactory ferritin levels and LIC as these give a false sense of security. The rates of iron accumulation seem to be different in the liver and the heart (7), while the MRI studies have shown that when chelation therapy is intensified, the rate of iron clearance between the two organs seems to be significantly different and the liver responds faster.

Echo studies
Doppler Echo and tissue Doppler studies can only identify the damage rather than delineating the cause, so limitation exists also in predicting iron load by Doppler Echo measurements. Structural and functional (systolic or diastolic indices) relationship to the amount of iron in the heart assessed by cardiac magnetic resonance imaging (CMR) was found, but these did not completely differentiate with specificity and selectivity the patients at risk for iron load. Therefore, echo techniques can select a number of patients who are at risk but they do not identify a large percentage of those. Doppler Echo remains an important monitoring tool for TM patients and should continue to be used (2).

Radionucleide cardiac scans (MUGA)
Resting or combined Resting-Stress radionuclear studies have been used for assessing left ventricular LV function in TM. Estimation of systolic function is more accurate than that assessed by echocardiography, especially during exercise stress, when an inadequate response to stress, indicative of subclinical cardiac dysfunction could be revealed. It is however time consuming, should not be performed frequently and has almost the same limitations as echo regarding the pathophysiology of the measured injury (2).

BNP levels
B-type naturetic protein (BNP), considered useful in predicting the risk of developing cardiac disease has no predictive value in TM patients, as it is only elevated in patients who had overt cardiac dysfunction and the levels do not reflect the severity of heart failure (8).

Cardiac magnetic resonance (CMR) imaging
CMR has revolutionized the approach to management of TM. A number of studies have demonstrated the value of CMR in indirect assessment of cardiac iron overload (T2*) and function parameters (9). CMR results are reproducible and robust, provided the T2* method is used and the area measured is the intraventricular septum. The major benefit from the use of MRI is that it allows the comparison of iron load to heart function. MRI provides also the ability to determine the predictive value of ferritin, LIC, echo and BNP with respect to cardiac iron. However, heart iron MRI measurements are limited to the deposited forms of ferritin and haemosiderin that comprises the majority of the cellular iron but it cannot measure the toxic LCI. Despite this, given the fact that a continuous interaction between the three forms of iron exists, MRI measurement remains the best method for estimating potential iron toxicity.
Chelation treatment of iron induced heart disease

Chelation treatment today should be guided by MRI findings, if the technique is available. In the presence of excess cardiac and or hepatic iron, treatment strategies include increase of the dose and/or frequency of desferrioxamine, switch to oral chelators (Deferiprone or Deferasirox) or to the combination of Deferiprone with Desferrioxamine, provided there are no contraindications to their use (10). Recent and ongoing studies have demonstrated that Deferiprone, a small molecule that permeates all tissues, is more efficient in removing cardiac iron and improving cardiac function than desferrioxamine. Some preliminary clinical and laboratory observations with Deferasirox are encouraging with respect to removal of cardiac iron. Renal dysfunction is rare in TM, however, it is important to note that adequate renal function is essential for the elimination of the chelators. Chelator adjustment will be necessary. Any treatment modification should be followed by close monitoring. In countries where MRI is not available, then all the patients’ traditional parameters need to be analysed, (ferritins, liver iron concentrations) as well as ECG and echocardiogram, taking into account the limitations. In patients who have been poorly chelated, the risk of chelation toxicity is minimal and would only be likely to occur after prolonged therapy, however, it is important to be vigilant for such complications. MRI is more necessary for those patients who have had good chelation therapy but who are at risk of chelation inadequacy with respect to the heart and for those who have had treatment modification in order to follow the efficacy of the changed chelation regime.

Conclusions

This formerly catastrophic genetic defect has been revolutionized with the availability of adequate chelation therapy and more recently with other important advances. It remains important, practically, to aim to maintain low LIC’s and ferritin levels, particularly as the latter are easily accessible and assessable. Similarly, echocardiography should remain a routine tool as it does have some predictive value and can also be used to monitor patients in whom intensification of chelation function has been instituted. Cardiac magnetic resonance imaging can be particularly helpful in identifying all TM patients at risk of developing heart disease by assessing the cardiac iron load. Chelation therapy can be tailored to remove the excess heart iron. Attention to patient’s continuous compliance with adequate chelation is mandatory.

References


Session 5 – Sickle Cell Disease

Current Understanding in the Management of Sickle Cell Disease
Adlette Inati, MD, Head, Division of Pediatric Hematology-Oncology; Medical Director, Children's Center for Cancer and Blood Diseases, Rafik Hariri University Hospital, Beirut, Lebanon

Sickle cell disease (SCD), the most common monogenetic disorder worldwide, represents a major public health concern because of its associated significant morbidity and mortality. Advances in molecular and cellular biology have resulted in an accumulation of data on sickle cell pathophysiology related to erythrocyte and extra-erythrocyte events. These emerging data have broadened our understanding of the complexity of this molecular disease with heterogeneous manifestations and have paved the route to the development of novel and targeted therapeutic interventions. Investigations have elucidated new risk factors or defined early risk prediction models which are vital for formulating optimal therapy. (1–4)

Clinical manifestations in SCD can be attributed to vaso-occlusion and to chronic haemolysis. Vaso-occlusive associated symptoms include: pain, acute chest syndrome (ACS), stroke, osteonecrosis, functional asplenia leading to life-threatening infections and organ failure. Chronic haemolysis produces a clinical sub phenotype characterized by anemia, pulmonary hypertension, priapism, leg ulceration, sudden death, and possibly stroke. There are now powerful data to implicate haemolysis-associated impairment of nitric oxide bioavailability in the latter sub phenotype. (1–3)

The development of several important interventional measures such as neonatal screening programs, penicillin prophylaxis and disease-modifying therapies has led to a substantial improvement in survival in affected patients. (5–11) As patients get older, however, new chronic complications are appearing. The main-stay of therapy in SCD is to prevent and treat complications. This is best achieved by reducing the amount of HbS through the prevention of polymerization and reversal of this process. For seriously affected children, three therapeutic options are currently validated: hydroxyurea (HU), transfusion/chelation therapy, and stem cell transplant (SCT). HU is an effective therapy for children and adults and works by reducing the adhesion of sickle red cells to endothelial cells and modulating endothelial cell activation and nitric oxide generation. This can lead to an increase in Hb and HbF levels, as well as a decrease in reticulocyte, white cell and platelet counts. HU therapy has been shown to reduce pain and
ACS, decrease the frequency of hospitalizations and the need for transfusions and attenuate mortality (7–8).

The use of transfusion therapy in SCD is increasing further to the findings of the STOP trials (9, 10) and there are expanding implications for the use of prophylactic blood transfusions. Based on Stop trials, blood transfusion therapy is now considered standard care for primary and secondary stroke prevention in children with SCD and transcranial doppler (TCD) screening is now recommended for all children with SS ages 2–16 years. The STOP I trial in children at high risk of stroke found that transfusion therapy reduced the rate of first stroke from 16% to <1% per year (9) while the STOP II trial observed a 34% reversion to high-risk of stroke in patients who discontinued transfusions compared with those who continued transfusions. (10) Transfusion is also indicated for various acute/episodic and chronic conditions.

Iron overload is a serious and inevitable consequence of regular transfusion therapy and whole body iron levels are a major determinant of morbidity and mortality in SCD. A number of studies have shown that iron chelation therapy is effective for reducing iron burden in patients with SCD. (1,2) Deferasirox (Exjade®, ICL670), a recently FDA approved once daily oral chelator, has been shown in randomized trial to be safe, convenient and efficacious. (11)

SCT remains the only available cure for SCD and is indicated for selected cases. This treatment offers a very high survival rate, with few transplant-related complications and with elimination of sickle related complications in the majority of patients undergoing this therapy. (12) Emerging novel treatments have evolved from our improved understanding of the biology of SCD and its new pathophysiologic model and include anti-sickling agents, prevention of red cell dehydration, nitric oxide and augmentation of fetal Hb (HbF). (1,3)

References

4. Inati A, Taher A, Bou Alawi W et al. Beta-globin gene cluster haplotypes and HbF levels are not the only modulators of sickle cell disease in Lebanon. Eur J Haematol 2003;70:79–83
Growth retardation occurs almost invariably in homozygous beta-thalassaemia. Significant size retardation is observed in stature, sitting height, weight, biacromial (shoulder) and bicristal (iliac crest) breadths. After the age of 4 years the longitudinal growth patterns display rates consistently behind those of normal controls. The bone age is frequently delayed after the age of 6–7 years. Growth retardation becomes markedly severe with the failure of the pubertal growth spurt. With the introduction of high transfusion regimes and efficient iron chelation prepubertal linear growth has been improved markedly. However, abnormal growth is still observed in the majority of patients during late childhood and adolescence. Haemosiderosis-induced damage of the endocrine glands is implicated to be one of the main causes for their growth failure. However, other factors could considerably contribute in the aetiology of this growth delay, including:

1. the effect of chronic anaemic hypoxia secondary to low haemoglobin concentration;
2. toxicity of desferrioxamine treatment;
3. increased energy expenditure due to high erythropoietic turn-over and cardiac work;
4. nutritional deficiencies including calories, folic-acid, zinc, and vitamin A;
5. disturbed calcium homeostasis;
6. bone disease; and
7. hepatic and pancreatic dysfunction.

Our studies were conducted to investigate the different factors that might contribute to growth retardation in children with thalassaemia to specifically answer the following questions:

1. Do children with thalassaemia have significant growth retardation and/or pubertal delay?
2. Are these patient undernourished? Do they eat qualitatively and quantitatively adequate food?
3. Do children with thalassaemia have significant impairment of hepatic functions? Is it related to the degree of iron overload and/or transfusion-associated hepatitis?
4. Do children with thalassaemia have abnormalities of GHI/IGF-I/IGFBP3 axis?
5. Does GH therapy increase linear growth in these patients? Do they have resistance to GH?
6. Do children with thalassaemia have abnormalities of the pituitary-thyroid and/or the pituitary adrenal axis?
7. Do children with thalassaemia have decreased bone mineral density (osteoporosis)?

Out of 120 children with transfusion-dependent beta thalassaemia on regular blood transfusion and sub-optimal iron chelation randomly selected from the haematology clinic of Alexandria University Children’s Hospital and Royal Hospital Muscat Oman were studied. 250 age and sex-matched normal children served as controls for the growth data. Forty-nine percent of children with beta thalassaemia on frequent blood transfusion and iron chelation are short (HtSDS <-2) and eighty-three percent of them had slow linear growth velocity (GVSDS <-1). Seventy-three percent of thalassaemic males above the age of 14 years do not have testicular development. Spontaneous menarche and breast development occur only in 26 and 42 percent respectively of thalassaemic females above the age of 13 years.

Children with thalassaemia have high prevalence of HBS antigenaemia and HCV antibody seropositivity (44.4 and 23.5 percent) compared to normal age matched children. Serum ALT concentrations are significantly correlated with HtSDS. These findings suggest that impaired hepatic function secondary to siderosis or chronic hepatitis might contribute to linear growth impairment. Our thalassaemic children have progressive and early dysfunction of pancreatic B-cells manifested by decreased insulin release in response to oral and i.v. glucose and arginine infusion, before the development of significant insulin resistance or impairment of glucose tolerance. They have significant hyperglucagonaemia not suppressible with oral glucose. The mechanism of B-cell dysfunction is mediated neither by ICA nor by cytokines.
Seventeen randomly selected thalassaemic children had significantly lower peak growth hormone response to provocation by clonidine and glucagon compared to normal short children with 20 children with constitutional delay of growth and puberty (CDGP) (p <0.005). The peak GH response to provocation by clonidine and glucagon was significantly low in thalassaemic patients. Seven, out of the 17 patients had classic GH deficiency (peak GH <7ug/L after provocation by clonidine and glucagon, with low IGF-I, and IGFBP3 concentrations). The other 10 patients, with normal GH response to provocation, underwent 12-h study of nocturnal GH release. Analysis of the pulsatile properties revealed that the integrated and mean GH concentrations over 12h were markedly lower in thalassaemic patients versus controls. Five out of the ten studied patients had maximum nocturnal GH peak below10 ug/L and four of them had mean nocturnal GH concentration below 2 ug/L. Two had severe neurosecretory dysfunction of GH secretion. Their circulating IGF-I and IGFBP3 concentrations were markedly reduced compared to those for controls. Thalassaemic patients had significantly lower circulating IGF-I and IGFBP3 concentrations compared with children with CDGP. The IGF-I and IGFBP3 responses to GH injection were significantly lower in thalassaemic patients compared to those with CDGP (n=20) and growth hormone deficiency (GHD) (n=20). Their serum IGF-I concentrations after stimulation with GH were still lower than the basal circulating levels for the controls (p<0.01). Treatment of short thalassaemic patients with human GH (20U/m2/week divided on 7 daily doses sc.) showed a significantly slower linear growth velocity in thalassaemic children versus those with normal variant short stature (NVSS) and those with GHD. The latter two findings suggest the presence of partial GH resistance in these patients.

Impaired GH secretion (deficiency or neurosecretory dysfunction) can explain in part the significantly lower IGF-I and IGFBP3 synthesis with subsequent growth impairment in children with thalassaemia major. However, haemosiderosis of the liver in these patients with disturbed hepatic function also decrease synthesis of IGF-I and IGFBP3. In our study serum ferritin concentration was significantly correlated with IGF-I concentration (r = -0.47, P<0.01) and IGFBP3 (r = -0.43, p<0.01). MRI scanning of the hypothalamic-pituitary area of thalassaemic patients showed many structural abnormalities including different degrees of pituitary atrophy and haemosiderin infiltration of the pituitary gland and midbrain. These structural alterations are correlated with defective spontaneous GH secretion in these patients. Measurement of bone mineral density (BMD) of 33 children with beta-thalassaemia, by dual photon absorptiometry, revealed significant reduction of their BMD (30% less) compared to average BMD for age- and sex-matched normal children, and significantly lower than 20 children with CDGP. BMD was correlated significantly with age, height, weight and BMI as well as with the circulating concentrations of IGF-I and IGFBP3 (p<0.01) and negatively with serum ferritin concentration. No significant correlations, was found between BMD on the one hand and PTH, PO4, Ca, or ALP concentrations on the other hand. In our study children with beta thalassaemia had significantly lower cortisol response to provocation with low-dose ACTH. Although iron deposition in the adrenals might be the cause of adrenal insufficiency, it has been shown that IGF-I enhances the steroidogenesis and ACTH responsiveness of human adrenocortical cells in culture. Deficiency of IGF-I synthesis in beta thalassaemia might contribute to the defective cortisol production and possibly other adrenal androgens which might explain the weakness, pigmentation and lack or delayed adrenarche in some thalassaemic patients.

Nutritional support of thalassaemic children, using high caloric diet, increased significantly their IGF-I concentrations and was associated with markedly increased weight gain and faster linear growth rate. Based on our studies our recommendations are:

1. Improvement of the quality and quantity of food intake in these patients to increase IGF-I and subsequently their growth.
2. Vaccination against hepatitis B and meticulous screening of blood before transfusion.
3. Close monitoring of linear growth and those with slow GV or HtSDS below -2r should be investigated for GH/IGF-I deficiency, thyroid function, calcium homeostasis and insulin secretion.
4. Short children with thalassaemia who have defective GH secretion and /or low circulating IGF-I should receive GH (and/or IGF-I) therapy to improve linear growth and increase bone mass. However, they may need supraphysiologic doses of GH to overcome their partial GH resistance.
5. Adolescents with delayed and/or failure of puberty should be investigated early for gonadotropin release and sex-steroid secretion. Those with hypogonadism should be treated early and adequately with sex-steroids to improve their pubertal growth spurt, bone accretion and sexual development and function.
References:


Current perspectives fertility and pregnancy in Thalassaemia

Rekha Bajoria, MRCOG, MRCP, PhD, Clinical Senior Lecturer in Medical Education / Consultant
Institute For Women’s Health, University College Hospital, Department of Obstetrics and Gynaecology, North Middlesex Hospital, London, UK

Introduction

Advances in the primary care of β-thalassaemia major by optimal blood transfusions and chelation therapy have improved survival of patients into adulthood. Therefore expectation to have a family is an important aspiration for a better quality of life. Although spontaneous fertility can occur in well chelated and transfused patients with spontaneous puberty, majority are infertile due to hypogonadotrophic hypogonadism (HH) and need assisted reproductive techniques (ART). I will report our experience of pregnancy including those following ART in thalassaemia patients. A brief outline on prenatal diagnosis will also be addressed and new perspectives of induction of gametogenesis including pregnancy care in patients with thalassaemia syndrome will be highlighted.

ART in 11 women with β-thalassaemia major over the last 15 years at the University College Hospital, London who had HH but functionally intact ovaries will be presented. The major pre-pregnancy issues including pre-pregnancy counselling, partner screening, medications, suitability for induction of ovulation and pregnancy care are reviewed. Pregnancy was advised when patients had echocardiographically normal resting left ventricular performance. Iron overload was assessed by cardiac and hepatic MRI.
Cardiac function, along with haematological, endocrine, and hepatic parameters were initially assessed and monitored throughout pregnancy and for 2 to 9 years post partum. All patients were screened for Hep B, Hep C and HIV prior to ART. Partners were investigated for haemoglobinopathy. Desferrioxamine or oral chelators were discontinued. Fourteen healthy newborn infants were delivered. There were 2 sets of twin and one set of triplet pregnancy. One patient developed thrombo-embolic episode, while 2 had pre-eclampsia. The mean serum ferritin concentration increased from pre-pregnancy value of 2,000 to 5,000 µg/L post delivery. Although no significant cardiac complications were encountered, the incidence of preterm labour and growth restriction were 3 fold higher than the background population. Elective caesarean section was performed in 73% of cases. None of the fetuses had congenital malformations. The mean fetal birth weight was 2.5kg. Breast feeding was encouraged in all cases. Chelation therapy was recommenced in the immediate post partum period.

Conclusion
In conclusion, pregnancy is feasible in women with β-thalassaemia with normal resting cardiac performance and optimized iron overload status. Our experience suggests that, with proper care and guidance, pregnancies in women with thalassaemia major are practical and can have successful outcome in specialist centres under a multi disciplinary team.

Osteopenia-osteoporosis syndrome in patients with thalassaemia
Ratna Chatterjee MD, PhD, MFFP, Senior Lecturer and Consultant in reproductive endocrinology of chronic and serious disease Departments Of Obstetrics and Gynaecology , University College Hospital, London, UK

Abstract
With increased life expectancy, thalassaemic bone disease including osteopenia osteoporosis syndrome (OOS) is a major cause of bone pain and fragility fractures especially of the lumbar spine which may be found in 70-80% adult patients with β-thalassaemia world-wide, accounting for significant bone morbidity. The causes of OOS in thalassaemia syndromes are multifactorial and include marrow expansion secondary to ineffective erythropiesis, anaemia, transfusional haemosiderosis, delayed puberty, use of desferrioxamine or oral chelation agents for iron overload. Multiple endocrinopathies such as hypogonadotrophic hypogonadism or primary hypogonadism, low IGF1, low vitamin D levels due to aberrant vitamin D-PTH axis are all responsible. Genetic factors, for instance polymorphism of the VDR gene and Colia 1 gene, may also play role in the development of OOS in thalassaemic patients. I will discuss the definition of osteoporosis, methods available for understanding the pathophysiology and role of Dexa scan, biochemical bone markers and histomorphometry in clinical diagnosis and also as research tools for current and future management of OOS. We shall also discuss the role of hypogonadism in the genesis of OOS and the scope and limitations of hormone replacement therapy and the role of bisphosphonate and other drugs in the management of OOS.

Session 7 – Liver Disease in Thalassaemia

Therapy of Hepatitis C in Thalassaemia
Ala’ I Sharara, MD, Professor of Medicine, Head, Division of Gastroenterology, American University of Beirut Medical Center, Lebanon; Associate Consulting Professor, Duke University Medical Center, USA

Although the natural history of HCV infection in thalassaemias is unclear, the morbidity and mortality of those patients is thought to be increased. Liver disease is more severe in HCV-infected patients and may be compounded by hepatic siderosis. Treatment of HCV in thalassaemia patients is aimed at viral eradication, improvement in liver histology, reduction of the risk of hepatocellular carcinoma, and improvement of health-related quality of life and survival. Initial studies using interferon monotherapy have shown a sustained viral response of ~30%. Although combination therapy of interferon and ribavirin has replaced monotherapy in HCV-infected individuals, the use of ribavirin in thalassaemics has been largely avoided because of ribavirin-associated haemolysis. Limited case series have, however, shown that the use of ribavirin with interferon is associated with a higher response rate but at the cost of 30% to 50% increase in transfusion requirements during treatment. Although peginterferon monotherapy is sufficient in acute HCV, combination therapy (pegylated interferon-2α and ribavirin) is superior to peginterferon
monotherapy resulting in sustained viral response in about two thirds of individuals infected with HCV genotype 1 or 4. A detectable viral RNA at 12 weeks of therapy is predictive of treatment failure. When compared with peginterferon monotherapy, the combination with ribavirin was associated with an increase in transfusion requirements but no other significant side effects. Importantly, response to interferon was unrelated to hepatic iron load.

HCV Infection in Thalassemia Major

**Blood transfusion**
- **Iron overload**
- **Liver inflammation**
- **Liver fibrosis**
- **Liver cirrhosis**
- **Antiviral therapy**
- **Chelation therapy**

**Suggested References**

**Session 8 – Thalassaemia Intermedia**

**Pathophysiology and complications of thalassaemia intermedia**

*MD Cappellini, C Cesaretti, RFasulo, Policlinico Foundation IRCCS- University of Milan, Italy*

**Abstract**
Thalassaemia intermedia (TI) encompasses a wide clinical spectrum of beta-thalassaemia phenotypes. Some TI patients are asymptomatic until adult life whereas others are symptomatic from as young as two years of age. A number of clinical complications commonly associated with TI are rarely seen in thalassaemia major, including extramedullary haematopoiesis, leg ulcers, gallstones and thrombophilia. Prevention of these complications, possibly with blood transfusion therapy, is ideal since they may be difficult to manage. Currently, many patients with TI receive only occasional or no transfusions, since they are able to maintain haemoglobin levels between 7–9g/dL; the risk of iron overload, necessitating adequate chelation therapy, is also a contributing factor.
Clinical definition of thalassaemia intermedia

Description of the various thalassaemia forms is based on the severity of the condition rather than the underlying genetic abnormality. Although the clinical phenotypes of thalassaemia minor, intermedia and major differ, there are some similarities. There is an increasing awareness of the need for accurate diagnosis in order to achieve optimal patient management and to avoid over or under treatment (1,2). In general, TI is characterized by Hb levels maintained around 7–10g/dL without the need for regular blood transfusions, by more severe red blood cell (RBC) abnormalities than thalassaemia minor, by a varying degree of spleen enlargement, and by skeletal changes such as expansion of the facial bones.

Molecular definition and Pathophysiology of thalassaemia intermedia

The beta-thalassaemias, including TI, arise from defective gene function leading to the partial suppression of beta-globin protein production. The extent of suppression varies from patient to patient and dictates the clinical severity of disease. Most TI patients are homozygotes or compound heterozygotes for beta-thalassaemia, meaning that both beta-globin loci are affected (1). Less commonly, only a single beta-globin locus is affected, the other being completely normal (3). The mild clinical characteristics of TI compared with thalassaemia major result primarily from three different mechanisms (1,4):

- Inheritance of a mild or silent beta-chain mutation. Rather than a complete absence of beta-chain synthesis, the level of synthesis is subnormal. This leads to a smaller imbalance between the number of alpha- and beta-chains compared with an absence of beta-chains
- Co-inheritance of determinants associated with increased gamma-chain production. The increased number of gamma-chains helps to neutralize the large proportion of unbound alpha-chains
- Co-inheritance of alpha-thalassaemia. This helps to suppress the synthesis of alpha-chains, causing less of an alpha/beta-chain imbalance.

The phenotype of TI may also result from the increased production of alpha-globin chains by triplicated alpha genotype associated to beta-heterozygosity (5,6), and from the interaction of beta and delta beta thalassaemia (7,8).

Clinical sequelae of thalassaemia intermedia

Three main factors are responsible for the clinical sequelae of TI: ineffective erythropoiesis, chronic anaemia and iron overload. The severity of clinical sequelae primarily depends on the underlying molecular defects. Alpha-chains are highly unstable and precipitate into erythroid precursors in the bone marrow, causing membrane damage and cell death – this is ineffective erythropoiesis (15). Hypertrophy of erythroid marrow in medullary and extramedullary sites, a consequence of severe ineffective erythropoiesis, results in characteristic deformities of the skull and face and may also cause cortical thinning and pathological fractures of long bones (2,9). The degree of ineffective erythropoiesis is the primary determinant of the development of anaemia, while peripheral haemolysis of mature RBCs and an overall reduction in Hb synthesis are secondary. Chronic anaemia leads to an increase in gastrointestinal iron absorption, resulting in iron overload that can cause a number of serious complications including cardiac failure and endocrine abnormalities such as diabetes mellitus and hypogonadism.

References

Thrombosis in thalassaemia intermedia

Ali Taher, MD, Professor of Medicine, Hematology-Oncology Division, Department of Internal Medicine
American University of Beirut Medical Center, Beirut, Lebanon

Abstract

Although the life expectancy of β-thalassaemia patients has markedly improved over the last few years, patients still suffer from many complications of this congenital disease. The presence of a high incidence of thromboembolic events, mainly in β-thalassaemia intermedia, has led to the identification of a hypercoagulable state in these patients. In this overview, the molecular and cellular mechanisms leading to hypercoagulability in β-thalassaemia are highlighted, with a special focus on thalassaemia intermedia being the group with the highest incidence of thrombotic events as compared to other types of thalassaemias. Recommendations for thrombosis prophylaxis in these patients are also discussed.

Overview

Patients with β-thalassaemia intermedia (TI) generally have a milder clinical phenotype than those with β-thalassaemia major (TM). The pathophysiology of TI is characterized by extravascular haemolysis, with the release into the peripheral circulation of damaged red blood cells and erythroid precursors because of a high degree of ineffective erythropoiesis. The life expectancy of β-thalassaemia patients has markedly improved over the last few years, as a result of regular blood transfusions and compliance with tight iron chelation therapies. However, β-thalassaemia patients still suffer from many complications of their chronic disease, and several serious previously undescribed complications are now being acknowledged. The presence of a high incidence of thromboembolic events, mainly in TI has led to the identification of a hypercoagulable state in thalassaemic patients. Venous thromboembolic events, such as deep venous thrombosis (DVT), pulmonary embolism and portal vein thrombosis have been observed. However, there are relatively few epidemiological data on the overall frequency of these complications. The largest clinical study to date, by Taher et al., on 8,860 thalassaemia patients (6,670 TM & 2,190 TI) demonstrated that thromboembolic events occurred 4.38 times more frequently in TI than TM (p <0.001), with more venous events occurring in TI and more arterial events occurring in TM. Moreover, patients with TI who developed a thromboembolic event were mostly splenectomized, non-transfused, and had a haemoglobin level below 9g/dL. The study described age beyond 20 years, splenectomy, family history and previous thrombotic events as the main risk factors for developing a thromboembolic event. (3) In another series of β-TI patients, 24 patients (29%) developed either DVT, pulmonary embolism, or portal vein thrombosis during a 10-year follow up. All patients except one had undergone splenectomy. (4) In a recent survey involving nine Italian paediatric thalassaemia centres, venous thromboembolism was observed in 4% of 683 patients with TM and in 9.6% of 52 patients with TI. (2) In a study done to assess the rate of brain damage in patients with benign haemoglobinopathies, 37.5% of patients with TI showed asymptomatic brain damage on magnetic resonance imaging (MRI). (5) More recently, unpublished data by Taher et al. observed a 60% rate of silent brain abnormality by MRI rising to 86.7% when combining MRI to position emission tomography (PET). Autopsy findings in thalassaemia patients have definitely established hypercoagulability as a pathologic state. Autopsy series in patients with TM and TI describe the presence of DVT, pulmonary embolism and recurrent arterial occlusion, with thrombi in small and large pulmonary vessels. (3) Thus, as a result of multiple recent clinical studies and laboratory data, thalassaemia has been referred to as a “hypercoagulable state”.

Pathogenesis

Guided by clinical observation, diverse factors contributing to the hypercoagulable state in patients with β-thalassaemia have been identified (Figure 1). (2) In most cases, a combination of these abnormalities leads to clinical thrombosis. Among cellular factors, platelet activation contributes to a significant extent. The medical literature is rich in evidence suggesting that patients with β-thalassaemia have activated
platelets. Moreover, flow cytometric studies have also confirmed the chronic platelet activation status. In β-thalassaemia, there is evidence of increased platelet aggregation, an increased proportion of platelets expressing CD62P (P-selectin) and CD63, and a shortened platelet survival due to enhanced platelet consumption (especially in splenectomized patients).(2)

Alteration in red blood cells (RBCs), namely the oxidation of globin subunits in thalassaemia erythroid cells, leads to the formation of hemichromes. Hemichromes bind to or modify various components of the mature red blood cell membrane, such as protein band 3, ankyrin, and spectrin. After the precipitation of hemichromes, heme disintegrates, and toxic nontransferrin-bound iron species are released from the heme disintegration. The resulting free iron catalyzes the formation of reactive oxygen species. Iron-dependent oxidation of membrane proteins and formation of red-cell “senescence” antigens such as phosphatidylserine cause thalassaemic red cells to be rigid and deformed and to aggregate, resulting in premature cell removal. Studies have shown that thalassaemic RBCs may be a source of negatively charged phospholipids, which can eventually increase thrombin generation. This was verified by experiments that showed that annexin V, a protein with high affinity and specificity for anionic phospholipids, could block the procoagulant effect of isolated thalassaemic RBCs. Several studies have demonstrated that RBCs from thalassaemic patients also show enhanced cohesiveness and aggregability. These abnormalities have been reduced to normal range after the patients have received a blood transfusion, which could partly explain why patients with TI who are not regularly transfused had a higher incidence of thrombotic events than in patients receiving regular transfusions.(2)

The finding of elevated levels of endothelial adhesion proteins (E-selectin [ELAM-1], intercellular adhesion molecule-1 [ICAM-1] and von Willebrand factor [VWF]) and vascular cell adhesion molecule-1 [VCAM-1] in thalassaemic patients suggested that endothelial injury or activation may be a feature of this genetic disease which also plays an important role in the recruitment of white blood cells and red blood cells and promote thrombosis at vascular inflammation sites, vessel obstruction, tissue hypoxia and death.(6) More recently, it was shown that microparticles of red blood cell origins were elevated in patients with TI vs. controls; these have a potential to aggravate thrombotic events.(7)

Clinical observations have suggested that splenectomy in TI can contribute to an increased susceptibility to thrombosis. The development of these complications has been ascribed to the presence of high platelet counts following splenectomy and/or to increased number of abnormal RBCs. In splenectomized TI patients, Thrombin generation was significantly higher than in control subjects and patients who had not undergone splenectomy.(4) From the available data, DNA mutations do not appear to play an important role in the pathogenesis of thrombosis observed in B-thalassaemia. In two studies from the Eastern Mediterranean region the presence of factor V Leiden, prothrombin mutation, and methylene tetrahydrofolate reductase (MTHFR) mutations was not significantly correlated with the thrombotic risk.8 However, many investigators have reported changes in the levels of coagulation factors and inhibitors in thalassaemic patients. Prothrombin fragment 1.2 (F1.2), a marker of thrombin generation, is elevated in TI patients. The status of protein C and protein S was investigated in β-thalassaemia in many studies and generally they were found to be decreased; this might be responsible for the occurrence of thrombosis in thalassaemic patients. The presence of anti-phospholipid antibodies (aPL) has been reported in the serum of β-thalassaemia patients. However, the exact nature of these antibodies and their relation to coexistent hepatitis C virus (HCV) infection is still under investigation. Other pathogenetic mechanisms have been correlated with hypercoagulability in thalassaemia and these include cardiac dysfunction, hormonal deficiencies and liver dysfunction.(2)

The pathophysiological roles of haemolysis and the dysregulation of nitric oxide (NO) homeostasis are correlated with pulmonary hypertension in sickle cell disease and in thalassaemia. Nitric oxide binds soluble guanylate cyclase, which converts GTP to cGMP, relaxing vascular smooth muscle and causing vasodilatation. When plasma haemoglobin liberated from intravascularly haemolysed sickle erythrocytes consumes NO, the balance is shifted toward vasoconstriction. Pulmonary hypertension is aggravated and in sickle cell disease, it is linked to the intensity of haemolysis. Whether the same mechanism contributes to hypercoagulability in thalassaemia is not yet known and needs to be investigated.(6)

Recommendations

Venous thrombosis is more prevalent in splenectomized TI patients who are not regularly transfused. The reduction of thromboembolic events in adequately transfused patients may be the result of decreased
numbers of pathological RBC exhibiting indices of membrane damage. It should be noted that the benefit of regular blood transfusions is appreciated in the more frequent thromboembolic manifestations in less developed countries with inadequate transfusion resources. The available data on the use of anticoagulants, antiplatelet, or other agents in β-thalassaemia are either lacking or involve small, poorly controlled and/or relatively low-quality studies. However, TI patients who experienced a thromboembolic event and received aspirin afterwards had a lower recurrence of thrombotic events compared with those who were not taking aspirin, although these differences were not statistically significant. (2)

Treatment with the fetal haemoglobin-inducing agents, hydroxycarbamide and decitabine, results in decreases in plasma markers of thrombin generation. Hydroxycarbamide, specifically approved for the treatment of sickle cell disease (SCD), may decrease coagulation activation by reducing phospholipid expression on the surface of both RBC and platelets and decreasing RBC adhesion to thrombospondin. In addition to being a NO donor, hydroxycarbamide may also decrease haemostatic activation by its effect in decreasing the white blood cell count and particularly monocytes that express transcription factor. Hydroxycarbamide is only rarely used in thalassaemia, these patients may experience the benefits because of similar mechanisms described in SCD. Another approach would be to correct the reactive oxygen species-induced RBC membrane damage using antioxidants, although this approach has not yet been verified in clinical trials. (2)

It may also be possible to design a thalassaemia-tailored thrombosis risk-assessment model (RAM) to estimate thrombotic risk as a function of intrinsic (e.g. thalassaemia type and number of circulating RBC) and extrinsic (e.g. infection, surgery, and splenectomy) factors. Moreover, tests for predisposing factors could also be performed, particularly in high-risk patients. If clinically verified, this type of model could serve as a guideline for possible preventative treatment to decrease the incidence of thromboembolic events, which can cause significant morbidity and mortality.

![Diagram of hypercoagulable state in thalassaemia](image)

**FIGURE 1 Factors contributing to the hypercoagulable state in thalassaemia**

References

Cardiac complications and their management in thalassaemia intermedia

Athanasios Aessopos, MD, First Dept. of Internal Medicine, University of Athens Medical School, Laiko Hospital, Athens, Greece

Abstract
Heart disease in thalassaemia intermedia (TI) has a different aetiology, pathophysiology and clinical presentation than thalassaemia major (TM). This brief review describes the cardiovascular complications that are seen in TI. Early application of regular blood transfusion therapy, combined with proper iron chelation, in TI patients may attenuate the pathogenetic mechanisms.

Introduction
Thalassaemia intermedia (TI) represents up to one fourth of β-thalassaemia patients and is characterized by a wide spectrum of different genotypes and a clinical phenotype ranging between the severe, transfusion-dependent thalassaemia major (TM) and the asymptomatic carrier state. In comparison with TM, TI patients have generally a later clinical onset with a milder anaemia that does not require transfusions, at least during the first few years of life.

Cardiovascular complications represent the primary cause of mortality and a main cause of morbidity both in TM and in TI. However, a diverse form of heart disease is usually present in the two conditions. The main pathogenetic mechanism in all forms of thalassaemia is the inherited haemoglobin defect (reduced synthesis of the beta globin chains), which leads to chronic haemolytic anaemia and hence chronic tissue hypoxia. This in turn motivates a number of compensatory reactions, including increased erythropoiesis with bone marrow expansion and increased intestinal iron absorption. The latter manifestations are completely or partially inhibited nowadays in TM, due to the early application of regular transfusion therapy, while in TI patients are still present. As a result, although TM is mainly characterized by left ventricular dysfunction caused by iron overload, heart disease in TI has a different aetiology, pathophysiology and clinical presentation.

Thalassaemia intermedia
Cardiovascular involvement in TI is mainly determined by two factors, the high cardiac output state, resulting from chronic, untreated tissue hypoxia and its compensatory reactions, as well as the vascular involvement, caused mainly by endothelial dysfunction and elastic tissue abnormalities, which in turn leads to increased pulmonary vascular resistance and increased systemic vascular stiffness. Consequently, both right and left ventricles have to maintain a high cardiac output level through a stiff vascular bed. Moreover, valvular abnormalities and iron overload may also contribute in part. The main clinical manifestation of heart disease in TI is the age-related pulmonary hypertension, found in up to 60% of cases, followed by right-sided heart deterioration and failure. Left ventricular systolic left ventricular function is usually preserved, but it may also be decompensated under conditions requiring excessive cardiac work load.
A wide spectrum of vascular complications, related mainly to elastic tissue defects and hypercoagulability, both associated with chronic haemolysis, have also been reported in TI, including thromboembolic complications, cerebral and gastrointestinal haemorrhages, anginal symptoms, aortic aneurysms and leg ulcerations.

Management

Modern regular blood transfusion and iron chelation therapy has dramatically improved survival and quality of life in TM patients. Traditionally, TI patients are started on regular transfusion therapy as soon as they develop severe disease complications, such as heart failure, bone fractures, or endocrine disorders. Bearing in mind the above, it seems that the early application of regular transfusion therapy, combined with proper iron chelation, in TI patients may attenuate the aforementioned pathogenetic mechanisms of chronic haemolysis, tissue hypoxia, high output state and hypercoagulability, and thus prevent cardiovascular injury. In any case, an individually-tailored therapeutic approach, that also requires the active patient's participation in the decision making process, may be the key to the current TI therapy.

References


Hydroxyurea in the management of thalassaemia intermedia.

Mehran Karimi MD, Professor of Pediatric Hematology-Oncology, Pediatric department and Hematology Research Center, Shiraz University of Medical Sciences, Iran
Abstract

Hydroxyurea (HU) is an antineoplastic agent that enhances fetal haemoglobin. The clinical significance induced by this compound is well known in sickle cell disease. This clinical significance could also be expected in β-thalassaemia patients. Although studies on β-thalassaemia major patients showed a significant result but this clinical responses is expected to be more in thalassaemia intermedia (TI) patients because of lesser α/β globin imbalance. Studies showed that HU therapy in TI patients has significant effects on increasing Hb levels that can cause reducing blood transfusion dependency and transfusion free in some patients, decreasing skeletal deformities and splenomegaly and increasing energy state. So HU therapy could be a useful alternative to blood transfusion in some TI patients.

Hydroxyurea

Hydroxyurea (HU) is an antineoplastic agent available for oral use as capsules. It is also known as hydroxycarbamide and marked as Hydrea® and Droxia®. HU is a virtually tasteless, white crystalline powder with a chemically formula of CH4N2O2. (Figure 1) (1)

\[ \text{Figure 1: Chemical structure of HU} \]

Mechanism of action

HU is an s-phase-specific and non-DNA-hypomethylating agent that acts by inhibiting ribonucleotide reductase (an enzyme that converts ribonucleotide diphosphatase to deoxyribonucleotides) leading to inhibition of DNA synthesis. (1,2) HU approved by FDA for treatment of patients with certain cancers such as chronic myelocytic leukemia. (1) It is sometimes used to treated psoriasis and also as an anti HIV regimen. (3,4) Another proved action of HU is promotion of fetal haemoglobin (HbF) production via reactivation of γ-genes as a result of mechanisms that are not well known. The clinical benefit of HU in patients with sickle cell disease and reducing the complications as well as the crisis attacks has been demonstrated. (5) FDA approved HU for use in adults with sickle cell disease who experience moderate to severe crisis to reduce the rates of these crisis and blood transfusion dependency.

HU use in β-thalassemia

Enhancement of HbF production by HU can also alleviate the symptoms in patients with β-thalassaemia, because the imbalance in the globin chains could be ameliorated by the newly synthesized γ-chains being able to neutralize the excess α-chains, which could potentially correct ineffective erythropoiesis. (6)

β-thalassaemia major

Blood transfusion dependency at regular intervals and iron overload are the main complications in β-thalassaemia major. As a result reducing the transfusions is valuable to increase safety and quality of life in β-thalassaemia major. Studies on the efficacy of HU in β-thalassaemia major showed a modest increase in Hb levels that cause to reducing blood transfusion dependency and lessley transfusion free. In our study in 2004, we showed a good response to HU in transfusion dependent β-thalassaemia patients in Iran that in whom the Hb level kept above 9.5 gr/dl without transfusion. (7) Table 1 shows the results of two newly studies in the efficacy of HU in β-thalassaemia major patients. Some studies showed that polymorphism for GγXmnI (Gγ-158 C>T), homozygous for β-globin mutations [IVS-II 1 (G-A) or IVS-I 5 (G>C)] and carry α-thalassaemia deletions have a strong influence on the clinical response to HU therapy. (7,8)

β-thalassaemia intermedia (TI)

TI is a clinical definition applied to patients whose clinical phenotype is milder than that of thalassaemia major. The clinical course of TI is characterized by several complications that can be prevented by an accurate follow-up. Despite chronic anemia, individuals with TI do not require transfusion, except in association with intercurrent illness. (9)
Clinical response to HU is expected to be more in TI because the α/β-globin imbalance is lesser. Many studies demonstrated this hypothesis. Although many of these studies included only small number of patients, we reported the clinical significance responses of HU in a larger group of TI patients from Iran. (9) In this report, we divided 163 TI patients in two groups according to blood transfusion dependency. Group I consisted of 120 TI patients who were received regular blood transfusion and group II consisted of 43 TI patients with long-interval blood transfusions or without any history of blood transfusions. All patients were treated with HU 8–12 mg/kg/d orally once a day. 149/163 (91.4%) showed response to HU. The mean Hb level in groups I and II during study were 9.5 gr/dl and 9.6 gr/dl respectively. HU also associated with a marked increased in MCV and MCH. After HU treatment, 97% of patients described an increase in exercise tolerance and sense of well-being compared to before treatment. We observed no significant facial changes after therapy, indicating disappearance of these changes. Spleen size in non-splenectomized patients during treatment with HU showed no change in size in 83% of patients. Table 2 shows the results of some other studies in TI. In addition we showed that HU therapy can cause to decrease complications of cardiac functions and reducing in pulmonary hypertension during HU therapy in TI patients. (10)

Adverse effects of HU
Adverse effects of HU have been reported in different parts of the body systems. (1) Table 3 shows the adverse effects of HU regarding the body systems. Studies showed that hematologic tolerance of HU is good by low dose of HU therapy in β-thalassaemia patients. (8) In a recent study, we evaluate the adverse effects of low dose HU (8–12 mg/kg/d) in TI patients who had been treated with HU for a period of 10 years. Most of recorded adverse effects were dermatologic, neurologic and gastrointestinal that none of them cause to discontinuation of therapy. There were not any reports of hematologic toxicity, bone marrow suppression or any secondary malignancies during HU treatment. HU is genotoxic and is thus presumed to be a human carcinogen. In patients receiving long-term HU for myeloproliferative disorders, secondary leukemia has been reported. Skin cancer has also been reported in patients receiving long-term HU. (1) These results showed that low dose HU therapy in TI may be well tolerated without serious side effects. Although nevertheless, the question about the safety of HU treatment in thalassaemia patients should not be considered closed and further studies regarding the long-term adverse effects of HU should be undertaken.

Conclusion
The patients with TI have some complications such as organomegally, osteoporosis, iron deposition and extramedullary haematopoiesis which decrease the quality of life in these patients. HU has good effects on increasing Hb levels in TI patients that can cause transfusion free in some patients, decreasing complications such as osteoporosis and extramedullary haematopoiesis, decreasing skeletal deformities and splenomegaly and increasing energy state. So it could be a useful alternative to blood transfusion in some patients because of the oral use, inexpensive cost, clinical and haematological responses.

Table 1: Results of two newly studies in the efficacy of HU in β-thalassaemia major patients:

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>HU dose (mg/kg/d)</th>
<th>Length of therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradi et al. Transfusion 2007</td>
<td>45</td>
<td>16.3±2.3</td>
<td>1 year</td>
<td>20(44.5%) good response with ↑1.5 gr/dl in Hb level</td>
</tr>
<tr>
<td>Korean et al. Am J Hematol 2008</td>
<td>11</td>
<td>10.9±3</td>
<td>46±25 months</td>
<td>9 good response with Hb level of mean 8.2±0.7 gr/dl and transfusion free</td>
</tr>
</tbody>
</table>
Table 2: Some studies about the efficacy of HU treatment in β-thalassaemia intermedia:

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients</th>
<th>HU dose</th>
<th>Length of therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixit et al Ann Hematol 2005</td>
<td>37</td>
<td>10-20 (mg/kg/d)</td>
<td>4-36 months</td>
<td>45.9% transfusion free or ↑Hb&gt;2gr/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.3%↓transfusion to 50% or ↑Hb1-2gr/dl</td>
</tr>
<tr>
<td>Mancuso et al Br J Haematol 2006</td>
<td>18 splenectomized untransfused</td>
<td>5-30 (mg/kg/d)</td>
<td>1 year</td>
<td>Mean Hb ↑ 1.5 gr/dl</td>
</tr>
<tr>
<td>Gamberini et al Pediatr Endocrinol Rev. 2004</td>
<td>6</td>
<td>1000 (mg/d)</td>
<td>3 months</td>
<td>↓ the size of extra medullarly haematopoiesis mass and cured leg ulcers</td>
</tr>
</tbody>
</table>

Table 3: Adverse effects of HU regarding the body systems:

<table>
<thead>
<tr>
<th>Organ site</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy (rare, in HIV)</td>
</tr>
<tr>
<td></td>
<td>Headache, convulsions</td>
</tr>
<tr>
<td></td>
<td>Drowsiness, dizziness, hallucinations</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Alopecia (rare)</td>
</tr>
<tr>
<td></td>
<td>Erythema, rash</td>
</tr>
<tr>
<td></td>
<td>Cutaneous vasculitis/ ulcers and gangrene</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis like changes</td>
</tr>
<tr>
<td></td>
<td>Nail changes</td>
</tr>
<tr>
<td></td>
<td>Radiation recall reaction (rare)</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Mild nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis (rare, HIV)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Stomatitis, gastric irritation</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
</tr>
<tr>
<td>Haematologic</td>
<td>Bone marrow depression (neutropenia, anemia, thrombocytopenia)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Megaloblastosis</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Liver failure (rare, HIV)</td>
</tr>
<tr>
<td></td>
<td>Abnormal LFT’s (rare)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Type III (serum sickness)</td>
</tr>
<tr>
<td></td>
<td>Hyperpyrexia (low risk)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td></td>
<td>Skin cancer</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Acute pneumonitis (rare), fibrosis</td>
</tr>
<tr>
<td>Other</td>
<td>Fever, chills</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Renal/metabolic</td>
<td>Elevated BUN and creatinine</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia , dysuria</td>
</tr>
</tbody>
</table>

References

Session 9 – Stem Cell Transplantation

Allogeneic stem cell transplantation (STC) in patients with β-thalassaemia: King Faisal Specialist Hospital and Research Center Experience
A Al Jefri, A Ayas, A Al Musa, M Al Mahr, M Al Saleh, S Rifai, R Sabbah, A Al Seraihy, A Al Ahmari, E Khairy, I Al Hassan, H El Solh. King Faisal Specialist Hospital and Research center (KFSH&RC), Riyadh, Saudi Arabia

Abstract
From Jan. 1998–July 2006, 62 SCT were performed on 60 patients with β-thalassaemia from HLA related match donors. The overall survival (OS) and event free survival (EFS) for all pts. were 94% and 77%. The outcome of allogeneic SCT in our experience is satisfactory with overall survival 92% and EFS 77%. Transplantation at a young age and mild disease offers the best outcome. More advanced disease is associated with higher rate of rejection and severe GVHD.

Introduction
β-thalassaemia disorders are chronic hereditary haemolytic anaemias, managed by life-long regular blood transfusions. Secondary iron overload is treated with iron chelators. Sequales of iron overload can result from repeated transfusions causing serious morbidity and mortality at a young age. The only potential curative therapy for such disorder is stem cell transplantation (SCT) from a haematologically normal donor. Conventional treatment with blood transfusions, iron chelation and management of the multi-organ complications, including the need for psychological and economic support cannot be adhered to in an optimal way by all patients. On the other hand success of SCT requires the availability of a suitable donor and carries with it economic considerations. The patient needs to have a good physical status. In addition there are several complications such as graft rejection (up to 39%), recurrence of the disease, acute graft versus host disease (GVHD) (25-50% of cases in HLA identical related donations and 70-90% of cases in unrelated donations), and chronic GVHD in 27% of cases. There is also a significant mortality associated with the procedure which may reach 21% in some categories of patients. The first successful transplantation took place in Seattle (USA) in 1981 (1). Much invaluable experience was gained in Pesaro (Italy) which led to the recognition of factors that could influence the outcome (2). This led to better patient...
selection and the adoption of SCT by many centres (3). In this article we describe the experience gained at the King Faisal Specialist Hospital and Research Centre in Riyadh.

Patients and methods

From January 1998–July 2006 patients who were referred to KFSH&RC for SCT and who had a fully match related donor underwent SCT. Sixty patients were transplanted from fully match related donors. All those were siblings except two paternal donors. A total of sixty two procedures were performed. Liver biopsies were not done routinely in those patients so disease severity was classified as mild, moderate or severe based on presence of hepatomegaly, Ferritin level, regular transfusion, and regular chelation similar to the modified classifications used in Seattle by Thomas et al (1). According to these criteria patients were classified as: mild, 23 patients. Moderate, 25 patients. Severe, 12 patients. Seven patients were reactive to Hepatitis C, four were RNA positive but all had no active hepatic disease. Donor matching was done by checking HLA Class I and Class II antigens with high resolution molecular studies. Patient’s ages ranged (1.5–13.9 years), median 5 years.

Transplantation conditions

BU/CY/ATG: from January 1998–March 2001, 24 pts. received Busulfan PO 4mg/kg/d x 4 days, cyclophosphamide IV 50mg/kg/d x 4 days, Equine ATG: IV 30mg/kg/d x 5 days. BU/CY: from June 2001 until January 2005, 38 pts. had Busulfan and cyclophosphamide in similar dosing and schedule. CY/TBI: for patients who had a second transplantation Cyclophosphamide: 50mg/kg/ d X 4 days, Total Body Irradiation (TBI) 200 cGy (fractionated ) twice a day X 3. (4, 5, 6, 7, 8)

Results

All patients had engrafted with ANC 0.5 X 109/L, median time 20 days (range 11- 29 days) and median time to self-sustained engraftment platelet count of 20X109/L 31days (range 16 -68 days). Chimerism studies in sustained engraftment, presence of donor’s cells (PMN/LYMPH cells) median 94% (range 59 %- 100%). Second transplants were performed on four patients and all engrafted. Three are disease free and healthy (Follow up 31, 39, 70 months). All had a different fully match sib for the second transplantation except one who rejected the graft of the same donor. The overall survival (OS) and event free survival (EFS) for all the transplanted patients were 92% and 77%. According to disease category, mild disease OS 96% and EFS 83%, while in moderate and severe disease OS 89% and EFS 73%. Five patients died (3 secondary to refractory severe GVHD). All seven patients with hepatitis C are alive with no active liver disease and are haematologically disease free except one who rejected the graft. Severe GVHD occurred in severe disease 25%, the moderate 20% and in the mild 13%. (9)

Conclusion

Allogeneic stem cell transplantation can be a curative therapy for patients with thalassaemia major who have an HLA fully match related donor. The outcome in our experience with paediatric patients is comparable to other major centres in the world. Standard conditioning regimens BU/CY or BU/CY/ATG can be used effectively in non advanced disease, younger age group. Severe/Chronic GVHD had a major impact on survival. Hepatitis C RNA positive (non-active disease) is not a contraindication for transplantation. A second transplantation can be successful if a different identical sibling is available. CY/TBI conditioning was useful and can be offered to mild / moderate risk category patients. (10)

Risk groups for patients with thalassaemia considered for treatment with SCT (Seattle Modified Classification):

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Good risk</th>
<th>Moderate risk</th>
<th>Poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver size</td>
<td>&lt; 2 cm below costal margins</td>
<td>&gt; 2 cm BCM</td>
<td>&gt; 2 cm BCM</td>
</tr>
<tr>
<td>Iron status</td>
<td>Regular program of chelation and serum ferritin &lt;2000 mg/dl (negative liver biopsy result)</td>
<td>Irregular program or no chelation give serum ferritin &gt;2000 mg/dl or positive liver biopsy</td>
<td>Irregular program or no chelation given ferritin &gt;2000 mg/dl or positive liver biopsy result</td>
</tr>
</tbody>
</table>

72
Thalassaemia Overall Survival 1998-2006:

![Graph showing Thalassaemia Overall Survival 1998-2006]

Thalassemia Event Free Survival 1998-2006:

![Graph showing Thalassemia Event Free Survival 1998-2006]

References

Eighteen years Hematopoietic Stem Cell Transplantation for beta thalassaemia major in Tehran

Ardeshir Ghavamzadeh MD, Kamran Alimoghaddam MD, Mohammad Jahani MD, Amir Ali Hamidieh MD, Seyed Asadollah Mousavi MD, Masood Irvani MD, Babak Bahar MD, Ali Khodabandeh MD, Farnaz Khatami MD. Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Shariati Hospital, Tehran, Iran

Abstract

Beta thalassaemia major is the most common type of haemoglobinopathy in Iran. We report here the results of 18 years Haematopoietic Stem Cell Transplantation (HSCT) in our centre.

Patients and Method

393 beta-thalassaemia major patients, 223 male and 170 female with median age of 6 years (range 2–28 years), have been transplanted from 1991 till March 2009 in our centre. One hundred seven patients were class one, 137 class two and 126 class three. They have received allogeneic transplantation from:

- 378 HLA fully matched siblings
- 9 HLA mismatched siblings, or other related donors
- 5 HLA full matched other relatives
- 1 HLA full matched unrelated.

Source of Haematopoietic cells were:

- 156 bone marrow
- 184 peripheral blood
- 9-cord blood
- 1 Bone Marrow combined Peripheral Blood
- 43 patients received mesenchymal cell in addition of Peripheral Blood (34 recipients) or Bone Marrow (nine recipients).

The most common conditioning regimen was Busulfan/Cyclophosphamide without Total Body Irritation and their Graft versus Host Disease (GvHD) prophylaxis regimen was Cyclosporine ± Methotrexate.

Results

Median time to Absolute Neutrophil Count ≥0.5×10^9/L was +15 and Median time to platelet count ≥20×10^9/L was +20. Acute GvHD occurred in 186 (47%) patients and chronic GvHD in 94 (24%) patients. Graft rejection occurred in 48 (12%) patients. 326 (83%) patients are alive and 67 (17%) dead. The most common cause of death was GvHD. 5 years overall (OS) and Disease Free Survival (DFS) were 78.6% and 68.5% respectively. The 5 years OS and DFS of patients with Peripheral Blood stem cell were 73.3% and 66.6%. The 5 years OS and DFS of Bone Marrow recipients were 83.6% and 72% respectively. There were not any significant differences in OS and DFS of patients in different sources of HSCT.
Conclusion
HSCT based on our experience and other documented studies is acceptable treatment for beta-thalassaemia major with better result in younger patients.

Session 10 – Molecular Therapeutic Potentials

Fetal globin Induction in β-Thalassaemia
Amal El-Beshlawy, Prof. of Pediatric Hematology, Cairo University, Egypt.

Summary
Thalassaemia patients with persistent high levels of fetal globin typically have less severe anemia, have milder clinical syndromes and are often transfusion independent. Reactivation of fetal haemoglobin could therefore benefit many patients. Different pharmacological agents have been studied, namely erythropoietin (EPO), short chain fatty acids (SCFADs) and cytotoxic agents, azacytidine, and hydroxycarbamid (HU) Variable results were detected, better with SCFADs and HU. Haemoglobin F inducers from natural plants angelicin and resveratrol are a powerful inducer of erythroid differentiation and increase of Hb F in erythroid progenitors of thalassaemia patients. Induction of Hb F in β-thalassaemia patients is expected to be crucial for developing countries unable to sustain the high cost of clinical management of β-thalassaemia patients.

Introduction
It is well established that thalassaemia patients do not become anaemic until fetal γ globin genes are developmentally silenced and that patients with persistent high levels of fetal globin typically have less severe anemia, have milder clinical syndromes and are often transfusion independent.(1) Reactivation of fetal globin could therefore benefit many patients even rendering them transfusion independent (2). Substances have been identified which can induce the production of fetal globin. Some of these are pharmacological agents, but some have been identified in the natural world. (3)

Haemoglobin F inducers

I – Pharmacological agents:

1. Erythropoietins (EPOs) preparations
2. Short chain fatty acids (SCFADs).

The mechanism underlying the pharmacological induction of Hb F synthesis include alteration of the chromatin structure to increase accessibility of transcription factors to promoters of the γ globin genes, such as inhibition of histone deacetylase (HDAC) activity (SCFADs)(4), hypomethylation of the gamma globin promoters (5), (5-azacytidines), inhibition of DNA synthesis (HU) and alteration of erythroid kinetics with acceleration of erythroid cell differentiation(6). Erythropoietins (EPOs): Because reports of suboptimal erythropoietin (EPO) response to anaemia in both sickle cell anemia and beta thalassaemia and indirect evidence that rapid erythroid expansion may favour Hb F production, there have been several studies to assess the effects of recombinant EPO in these disorders either alone or in combination with HU. Although the results have been variable with increased haemoglobin levels in some patients with thalassaemia intermedia yet there are potential risks from erythroid expansion causing increased iron absorption and extramedullary haematopoiesis (1) (7).

Short Chain Fatty Acid Derivatives (SCFADs)
Of the SCFADs and HDAC inhibitors, sodiumphenylbutyrate (SPB) increases Hb by 2.1g/dL in 50% of untransfused subjects (8). The most effective compound is arginine butyrate administered intravenously has increased total haemoglobin levels by 1-5 g/dL when administered at least for 3 months (9). Response to arginine butyrate has rendered patients transfusion independent. Isobutyramide administered for 4 weeks to thalassaemia intermedia patients has increased HBF and has decreased transfusion requirements in thalassaemia major (10). A prototype SCFAD, RB7, belonging to a new generation of fatty acid
derivatives, which has higher potency in inducing HbF synthesis than butyrate taken orally and is active at low concentration (11).

**Cytotoxic agents: 5-azacytidine and decitabine**
A small number of patients with beta-thalassaemia treated with 5-azocytidine showed an increase in gamma globin mRNA synthesis, normalization of globin chain imbalance and increase in Hb concentration (12). This drug is potentially toxic and hence few studies alone or combined with phenylbutyrate in severe beta thalassaemia has been done. More recently, decitabine has been studied as a pharmacological inducer of HbF in sickle cell disease (13).

Hydroxyurea (HU) is a chemotherapy which acts by inhibiting DNA synthesis without interfering with RNA or protein, it is used to control the painful crisis of sickle cell disease. A relatively small number of studies suggested a modest response to HU therapy in beta thalassaemia. More recent investigations have revealed that some transfusion dependent patients can become transfusion-independent following HU therapy. (14) Koren 2008 reported that 9 out of 11 thalassaemia major patients became free of transfusions and the majority of responders were either homozygous or heterozygous from the XmnI polymorphism. The use of HU in thalassaemia intermedia in paediatric and adult patients revealed a good response with increase of Hb more than 2g/dL in a good number of patients in different studies(15)(16). No correlation between the response to HU and specific beta thalassaemia mutations (Koren 2008, El Beshlawy 2008, Taher 2006, Karimi 2005, Dixit 2005, Yavarian 2004).

Supportive measures affect the activity of Fetal Globin inducers:
First folic acid should be given and iron supplementation in patients with ferritin levels < 1000ng/ml. Endogenous iron stores are not readily mobilized to support new erythropoiesis. Second patients do not respond to fetal globin inducers for 3-4 months following blood transfusion. Apparently these agents cannot act efficiently when the erythroid marrow is suppressed by transfusion. Third removal of imperfect thalassaemic red cells by the spleen can confound responses as only splenectomized patients responded to EPO in some trials. (1)

II – Hb F inducers from the natural world:
Compounds derived from biological materials such as fungi, plant extracts and agro-industrial materials are able to stimulate production of Hb F in adults:

Angelicin an extract from Aegle marmelos plant and Angelica arcangelica is a powerful inducer of erythroid differentiation, increases Hb F in erythroid progenitors from normal subjects and increase of γ globin mRNA in erythroid precursors isolated from thalassaemia patients.

Resveratrol: A Hb F inducer mimicking the biological activity of HU. It is present in wine, preferentially in the skin of grapes. It induces increase of γ globin mRNA in human erythroid precursors. It is a strong inducer of Hb F.

Rapamycin: isolated from a strain of streptomyces hygrosopicus found in soil from Easter Island. It has been approved by the USA FDA for prevention of acute rejection in renal transplant recipients. It increases HbF production in cultures of erythroid precursors from beta thalassaemia patients (3). Induction of Hb F from the natural world is not associated with cytotoxicity or cell growth inhibition (17). Induction of Hb F in beta thalassemia patients is expected to be crucial for several developing countries unable to sustain the high cost of clinical management of beta thalassaemia patients.

Gene therapy and bone marrow transplantation are interesting strategies but are useful for a minority of patients.

**Conclusions**
- Induction of HbF in β-thalassaemia patients is expected to be crucial for several developing countries who are unable to sustain the high cost of the clinical management of thalassaemia.
- Hydroxyurea seems to have an important role in the management of thalassaemia, especially intermedia, but long term follow up is needed to prove its safety.
- Oral butyrate is a good option for the management thalassaemia, especially intermedia, but more studies are needed to define the proper drug regimen.
• Induction of HbF by substances derived from the natural world is a promising option but again clinical studies are needed to prove efficacy and safety.
• The use of HbF inducers can help to reduce the risks to patients from blood transfusion, especially in developing countries.
• Gene therapy and bone marrow transplantation are interesting strategies but are useful for a minority of patients.

References
Session 11 – Reference Thalassaemia Centres

Requirements for a reference or expert thalassaemia centre: the structure/model for centres dealing with chronic/hereditary blood disorders

M Angastiniotis, A Eleftheriou, Thalassaemia International Federation

Summary

Chronic disorders, such as the haemoglobin disorders, which have a multi-organ involvement and are subject to complications, require multidisciplinary care. Most convenient for the patient is the concentration of expertise under one roof and where routine care, such as blood transfusions can be provided away from acutely ill patients with episodic infections and other conditions. These specialised centres already exist but as yet the standards which should designate a centre as an expert centre or a reference centre, have not yet been specified or applied. This article examines standards which have been described by two separate authorities in the USA and Europe, and suggests the application of these standards to existing or proposed haemoglobinopathy centres.

Introduction

It is recognized that all chronic conditions present a common set of challenges, because patients and families must deal with symptoms (such as pain in sickle cell disorders), disability, emotional and other psychological reactions which require adaptation and coping, complex and difficult medication regimens (such as the daily subcutaneous infusions of chelating agents in thalassaemia major), difficult life style and social adjustments and the need for specialized multidisciplinary care. Another added requirement compared to acute medical conditions, is the contribution of the patient to the management of his/her condition. The patient lives with his/her condition daily, while the health care professional deals with it periodically. The patients must therefore have the confidence and skills to manage their condition under the appropriate guidance and contribute to treatment decisions. Health workers, in their turn, need to learn different practices and require continuing education.

Thalassaemia care in many countries has achieved survival of thalassaemia patients well into adult life mainly by adopting good blood transfusion and chelation practices but also by adopting follow up protocols which aim to detect early and prevent if possible complications to vital organs (1,2). Optimum treatment will also improve quality of life which in addition to avoiding complications can be achieved by making psychosocial support a priority in management. With these requirements in mind, there is a recognised need for centres where the various specialties are gathered under one roof so that the patient can find all the services without moving from department to department or from hospital to hospital, and where the multidisciplinary team can interact, together and with the patients, and patients can receive treatment away from the acutely ill patients. In such centres expertise can be focussed on the complex management of the haemoglobin disorders. If patients, because of distance must be treated also in secondary and/or primary care centres then the expert centre becomes a reference centre and can offer shared care in partnership with the peripheral centre.

What then makes a centre an expert or a reference centre?

In Europe the following conditions were suggested by the Rare Diseases Task Force for the designation of a reference centre (3) and these may serve as standards which can be followed by haemoglobinopathy centres:

1. The capacity to provide expert diagnosis or confirmation of diagnosis
   This implies a reference Haemoglobinopathies laboratory which at least adheres to the best practice guidelines (4). It also means specialised clinical support services such as biochemistry, endocrine investigations, cardiological monitoring with echocardiography and magnetic resonance imaging and other specialised tests. The clinicians must also be able to recognise and diagnose significant events and complications

2. The capacity to provide expert case management
   This requires several conditions:
   a. Adherence to good practice guidelines, including protocols and clinical guidelines.
   b. Provide expert advice, including information to patients and genetic counselling.
c. Multidisciplinary approach, which is basic in caring for multi-system, chronic disorders such as thalassaemia and sickle cell disease.

d. Psychosocial support which is vital in any chronic disorder.

e. Staff patient ratio – this was arbitrarily set as 1 doctor per 50 patients in thalassaemia by the WHO advisory group several years ago.

3. Implementation of outcome measures and quality control
This implies maintaining a registry of patients and monitoring results through age distribution, survival data, the number of new cases per year, auditing haemoglobinopathy related deaths, monitoring population screening and prenatal diagnosis programmes, complication rates, quality of life outcomes. A list of indicators of monitoring evaluating outcomes should be agreed by the expert centres.

4. Sufficient activity and capacity to provide relevant services at a sustained level of quality
Quality cannot be assured if a clinic sees few patients and a laboratory few requests. What, however, is the minimum throughput required to designate a clinical and/or laboratory haemoglobinopathy centre expert is not clarified.

5. High level expertise and experience
To determine this it is necessary to investigate such parameters as:
   a. The grades and specialities of doctors/nurses.
   b. The number of years they have been involved in managing patients
   c. Publications and grants
   d. Strong contribution to research
   e. Teaching and training activities

6. Involvement in Epidemiological surveillance

7. Close links and collaboration with other expert national and international centres and capacity to network.

8. Close links with patients associations

An expert reference centre for haemoglobinopathies should meet most of these criteria. However, a reference centre, apart from dealing with cases and projects in its catchment area, is expected to accept referrals and provide assistance to secondary and primary health care providers. This is particularly important in large countries where patients, are scattered geographically, often located far from the reference centre. This requires routine care from the secondary or peripheral services, and collaboration with primary care providers. The links and networking of the reference centres, their position within the health service structure, must also be described since their effectiveness is also influenced by their outreach.

From this set of criteria the planning of a centre can be developed according to local conditions. A useful guide is also provided in Chapter 17 of the Guidelines for the Clinical Management of Thalassaemia Issued by TIF in November 2008 (2nd revised edition) (5). Beyond these basic standards other suggestions are offered by the chronic care model (CCM) which was developed by Dr Wagner of the MacColl Institute in Seattle, USA (6,7,8) The elements making up the CCM have been described under six headings: Health Care Organisation; Community Resources; Self-management support; Delivery system design; Decision support and Clinical Information Systems.

1. Health care organisation
Reference centres for chronic disorders need to be supported by the health system and administration. The thalassaemia centres created in the Southern European countries in the 1970s, were part of a nationally planned program of control which included both prevention and patient care. As such, they required both political will and budgetary support. Expert reference centres likewise require the same political and financial support, and especially need leadership to effect the improvements that are required and to acquire the resources (including the manpower) to implement these improvements.

The reference centre is part of the health system as a whole, but also part of the community. It requires support and recognition from both in order to succeed in its role, and to interact effectively with other parts
of the health system. To quote the Wagner experience in a recent publication (2001): “the visible support and promotion of the chronic disease improvement project by organisation leaders was a major predictor of success”, conversely “lack of leadership support or turnover in leadership where prime predictors of failure.”

Leadership should come both from health administration but also at the level of the reference centre, in which clinical leaders are visible, dedicated members of the team. They should promote effective improvement strategies and aim for safe, high quality care.

2. Community resources
The community is an important resource to support patient needs. The community includes school, support organisations such as the thalassaemia associations and other agencies outside the reference centre which could provide assistance to the patients or be supportive in the effort to integrate and lead as normal a life as possible. The reference centre should maintain links to these agencies.

Community linkages are particularly relevant to health education activities and genetic prevention programmes.

Obtaining resources such as blood donations form the community is another relevant link to the thalassaemia centres. In Cyprus for many years the blood donation services were voluntarily manned by parents of the patients so that the extra requirements of patients are met (Cyprus requires 1.5 timed more blood than low prevalence countries)

3. Self-management support
Self-management is of major importance in chronic disorders. Patient empowerment and the acquisition of self-management skills encourages adherence to treatment. The patient’s role in maintaining health and preventing complications in haemoglobin disorders is well recognised. The patient in partnership with the management team should set goals, establish action plans, identify barriers and present solutions. This relatively new role of the patient requires education which cannot rely solely on printed or other material, but rather on person-to-person education, which is sustained over a period of time. Both internal and community resources may be required to achieve these goals and leadership support is also required to ensure health workers’ time in this endeavour. Education for this new relationship should be extended to the health care staff, especially the doctors who often pay lip service to the partnership model but in practice expect a directive role, based on their superior knowledge of medicine without recognising their lack of understanding of the patient’s fears, prejudices, beliefs about medication and so many other issues that motivate the patients to either comply or rebel at the measures that are imposed on them “for their own good.” The reference centre is expected to understand these issues and emphasize the patient’s central role in managing his or her health, and also to organise internal and community resources (such as the support groups) to provide ongoing self-management support. This need to change physician attitudes, aiming at a new doctor/patient relationship is recognised in this project and the needs for a new approach to health worker education is examined in a work package on education. Routine assessment of self-management will be attempted through the outcome measures which also are the subject of a separate work package.

4. Delivery system design
High quality chronic care requires planning and coordination of the multidisciplinary team. In this team the roles must be clearly defined and collaboration assured so that evidence based clinical guidelines are adhered to, regular follow up is maintained and patient support and education are assured. Collaboration with primary care services is part of planning as is improved management of the system’s resources.

5. Decision Support
Evidence-based guidelines for the clinical management of both thalassaemia and sickle cell syndromes exist and are regularly updated. These include:

1. Guidelines for the Clinical Management of Thalassaemia – Published by TIF
2. Prevention of Thalassaemia and other Haemoglobin Disorders – Published by TIF in 2 volumes (2003 and 2005).
3. Management of Sickle Cell Disease – Published by NIH 2002
4. Best Practice Guidelines for Carrier Diagnosis for Carrier Identification and Prenatal Diagnosis of Haemoglobinopathies – Published by the European Molecular Genetics Quality Network (EMQN) in 2002.

Such guidelines should be available to all reference centres. The medical and paramedical staff should be regularly trained in the use of protocols and in sharing the information with patients to encourage their active participation to the decision taking process. Decision support can be further enhanced through electronic infrastructure with interactive facilities, such as the Ithanet portal which is being developed to include specialist and non-specialist exchanges and facilities such as telemedicine.

6. Clinical information systems

Using technology to organise data for more efficient and effective care, by monitoring patient health status to recognise complications early. Such electronic patient records can facilitate patient care planning and provide timely reminders to follow guidelines. Patient sub-populations of at-risk cases can be identified early for proactive interventions. Information can be shared with patients so they can be active contributors to their care. An electronic patient registry is a valuable tool for monitoring and measuring outcomes. For thalassaemia management such electronic records are available and used in several centres across Europe. In Italy for instance, a programme called Webthal is favoured, in Greece a database called JAnaemia is used, while some centres have locally developed databases.

Conclusions

Recognising these standards for patient care is needful not only for health planners and providers but also for support organisations. Do they constitute an ideal which cannot be reached especially in poorly developed economies where limited resources must be distributed to meet many other needs? In developed economies where haemoglobin disorders are rare diseases as they are in north European countries but affect immigrant groups will the resources be allocated and will they receive the attention they deserve?

These questions are difficult to answer but quality of care is an ethical requirement in any setting and in any country. The aim of care must be good quality of life and this in thalassaemia means maintaining a good clinical condition, providing psychosocial support, considering the implications of poor endocrinological control, such as poor growth, hypogonadism, bone disease, but above all recognising the patient’s right to a normal life, including education, employment, marriage and reproduction. If we know what we must aim for we can plan to achieve it and we can collaborate as health providers and as patient groups to make improvements. The focus of health services is the patient and economy must bow to his/her needs even in a world which is not ideal and squanders resources in many directions that are less important.

References:

Dear Dr. Taher,

Thank you for submitting your application for accreditation by the European Hematology Association Continuing Medical Education Unit.

We are pleased to inform you that your application has successfully passed the peer review process and that the following CME activity has been awarded EHA-CME accreditation:

Title of CME activity: 1st Pan-Middle East Conference on Haemoglobinopathies
Date of CME activity: May 1-2, 2009
Credit Points awarded: 12

Important Notes:
- It is the responsibility of the organizer to inform the participants of the EHA-CME accreditation and the instructions on how to claim their credits.
- All participants may print a European Hematology Association CME System approved CME certificate indicating the number of EHA CME Credit Points awarded, directly from the system on the CME section of the EHA website at www.ehaweb.org.
- An EHA-CME Credit Point account will be used by all interested participants. The organizer is required to convey a complete electronic list of participants including their first name, last name, and unique login code (usually the registration number) on the last day of the CME activity, this in order to activate the online evaluation.
- It is the responsibility of the organizer to comply with European Hematology Association CME Standards & Guidelines.

Please do not hesitate to contact cme@ehaweb.org if you have any questions regarding the accreditation of this CME activity.

Sincerely yours,

Francesco Lo Coco
CME Unit Chair

Willem Fibbe
President EHA

EHA EXECUTIVE OFFICE
Westblaak 71
3012 KE Rotterdam
The Netherlands
info@ehaweb.org
www.ehaweb.org
Tel: +31 10 436 17 69
Fax: +31 10 436 18 17