



Ironing Out Thalassemia

The high prevalence of the inherited blood disorder, thalassemia, in the Middle East and North Africa region makes it fertile ground for clinical studies. However, with transfusion-based treatments increasing the risk of iron overload to patients, researchers must look for new options

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A ground-breaking precedent was set by the US in 1983 when the Orphan Drug Act came into effect. Similar legislation was later adopted by Japan, Australia, Singapore and Europe – increasingly placing orphan drug development under the spotlight.

Today, there has been a marked industry shift towards this previously neglected area of research, with an uptake in clinical trials in rare diseases and the worldwide orphan drug market expected to grow significantly through this decade. But there is still much to do.

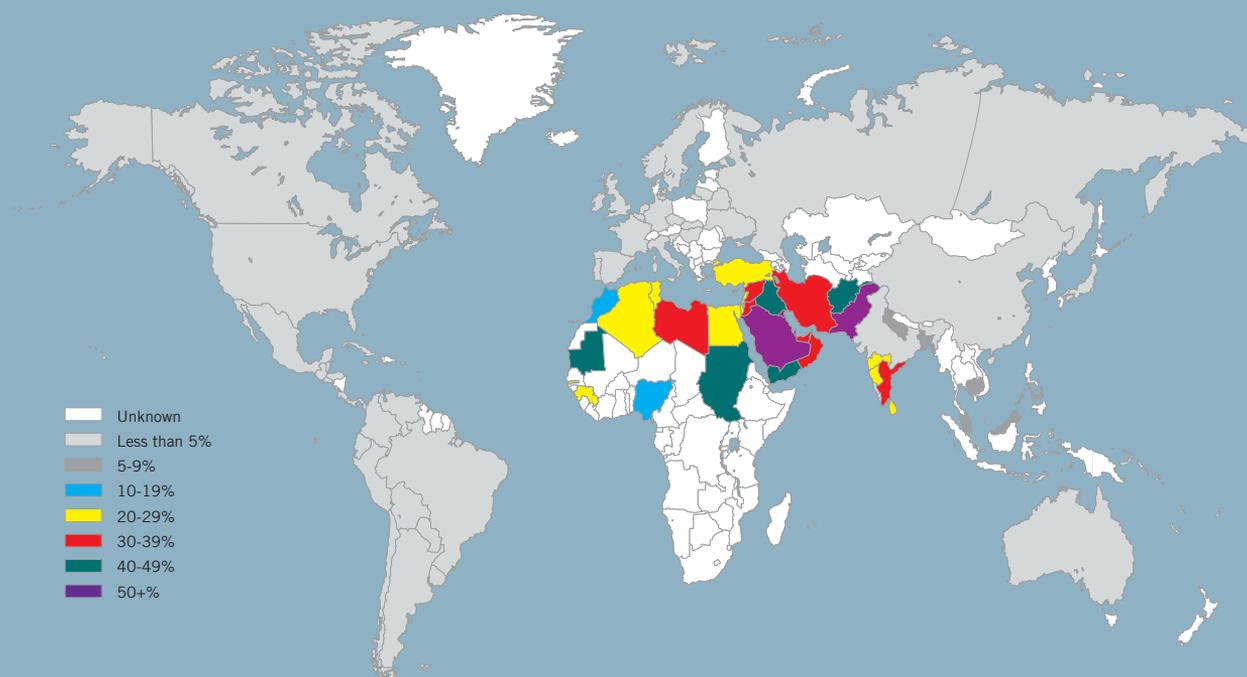
One indication that requires fresh impetus is haemoglobinopathies – genetic defects that result in an abnormal structure of one of the globin chains of the haemoglobin molecule. These are the most common inherited disorders in the Middle East and North Africa (MENA) region. Of these blood disorders, paramount importance needs to be focused on thalassemia, a genetic disease with early mortality that has life-long implications for patients and families.

Limited Treatment Options

Thalassemia is caused by diverse mutations of the alpha or beta globin genes that lead to anaemia. There are two main types of thalassemia: alpha thalassemia occurs when a gene or genes related to the alpha globin protein are missing or changed (mutated); beta thalassemia occurs when similar gene defects affect production of the beta globin protein. There are many forms of thalassemia and each has various different subtypes.

The unmet medical need in transfusion-dependent beta thalassemia is significant because current treatment options are mainly limited to blood transfusions and iron chelating agents, which are associated with toxicities. Repeated blood transfusion may lead to iron overload and many patients may also suffer from multiple organ dysfunction, largely due to excess iron deposits. Iron overload can lead to heart failure, liver fibrosis and diabetes. As a result, there is a need for researchers to work together to find new treatments for thalassemia.

Figure 1: Percentage of consanguineous marriages (1)



Disease Prevalence

Alpha thalassemia is prevalent in Southeast Asia, the Middle East, China and Africa, whereas beta thalassemia is prevalent in the Mediterranean region and, to a lesser extent, in Chinese, other Asians and African Americans. In the MENA region, countries such as the United Arab Emirates, Saudi Arabia, Lebanon, Jordan, Egypt and Tunisia have high prevalence of beta thalassemia.

Consanguineous marriages, where a union is formed between two individuals who are related as second cousins or closer, are common in these regions (see Figure 1 on page 66) and have been identified as one of the major causes of genetic disorders (1). Bittles *et al* have described the mounting public importance of congenital and genetic disorders in offspring. This has been observed from the increasing number of couples in highly consanguineous communities seeking counselling, as they are becoming more aware that consanguineous unions lead to increased expression of autosomal recessive disorders (2).

Centres of Excellence

Studies have shown that investigator-dependent factors, harmonisation and ease of approval dominate trial site selection (3). When selecting centres of excellence for clinical trials in thalassemia, it is essential that sites are able to provide standard care to thalassaemic patients and have infrastructure available to be able to make the right diagnosis. This can be achieved through family history, transfusion history, and physical and laboratory exams. As diagnosis is largely a clinical decision, specialists in the field of haematology should provide care to the patients.

Each site should have a formalised system for specialised thalassemia services that is appropriately configured to the geographical location and size of the patient population. In cases where patients live at some distance from the centres, transportation should be provided for study-related visits.

The availability of a facility for hospitalisation of the patients in the trial is an important point to be considered in the study. Sometimes the centres provide only day care to the patients and transfer them to hospitals should hospitalisation be required.

It is imperative to have a patient-focused approach in the management of these patients as they undergo regular blood transfusions and require easy access to blood donation centres. A premarital screening programme and genetic counselling for patients and their family members is essential to help them cope with the disease. Moreover, culturally sensitive genetic premarital and preconception counselling should be part of the training for healthcare providers, particularly in highly consanguineous populations.

Implementing Clinical Trials

Planning and implementing thalassemia trials in the MENA region must take into account the differing cultural, scientific,

ethical and logistical issues present in each country. There is a need to study the epidemiology of the disease across different nations in this region.

Of course, ensuring that countries with a significant prevalence of thalassaemic patients are included in the trial is an obvious step. This will help avoid transportation of patients from one country to the other, and minimise complicated accommodation and logistics support for patients and their caregivers, visa requirements, concerns with medical insurance, possible translations, and the follow-ups that are required once the patients return to their home countries.

Identifying and setting up the right sites is as important as recruiting and retaining patients. Furthermore, as in any emerging market, regulatory intelligence and local expert advice are key factors to consider due to the regulatory reforms taking place.

In addition, it is important to seek advice on regulations when conducting trials in the paediatric population; most cases of thalassemia are diagnosed within the first two years of life. A significant percentage of patients may be excluded in trials that enrol patients of 18 years and above. In the new era of 'expert patients', it is recommended to focus on patient advocacy groups for expert advice and to boost recruitment.

Fast Track Development

The US Food and Drug Administration's (FDA's) Fast Track initiative facilitates the development of drugs intended to treat serious or life-threatening conditions that have the potential to address unmet medical needs (4). A drug programme with Fast Track status is afforded greater access to the FDA for the purpose of expediting the drug's development, review and potential approval. Incentives for companies include extended market exclusivity, development cost assistance, waiver of some fees and review of applications within six months.

Different approaches to expedited approval include:

- Fast track approval for drugs that treat serious conditions and for which non-clinical or clinical data demonstrates the potential to address an unmet medical condition
- Accelerated approval for drugs that treat serious conditions, provide meaningful therapeutic benefit over available therapies and demonstrate an effect on a surrogate end-point that is reasonably likely to predict clinical benefit
- Priority review for drugs that offer major advances in treatment over existing therapies or provide a treatment where no adequate therapy exists
- Breakthrough therapy for drugs that treat serious conditions and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies

In the MENA region, it is possible to seek fast track approval from the ethics committees and regulatory authorities for investigational products that have been

granted orphan drug designation. However, these requests are reviewed on a case-by-case basis.

Chelation Therapy

Disease management for beta thalassemia includes regular blood transfusion. This helps prevent severe anaemia and allows for normal growth and development. Chelation therapy initially involved the use of desferoxamine, usually administered five nights per week over a period of several hours with an automatic pump used during sleep or taken anywhere the person goes. Advances have now been made in transfusion and chelation, with current chelation therapy focusing on the use of oral iron chelators, such as deferiprone and deferasirox.

Pressing Ahead

Despite significant steps being taken in the last few decades to improve survival and reduce complications with the introduction of the chelating agent, there continue to be major obstacles to effective treatment and prevention of thalassemia – namely, management of iron overload. Current treatments allow thalassemia patients to live relatively normal lives, but increased awareness is key to preventing inheritance of the disease.

The clinical research community should press ahead to further improve the management of patients with this rare disorder,

so they are able to have access to diagnosis, care and therapy that can make a difference.

References

1. *J Community Genet* 3(3): pp185-192, July 2012
2. Bittles *et al*, 1991; Tadmouri *et al*, 2009; Bittles and Black, 2010; Hamamy *et al*, 2011
3. Factors influencing clinical trial site selection in Europe: the survey of attitudes towards trial sites in Europe (the SAT-EU Study), *BMJ Open*, 2013
4. Visit: www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm

About the author



Rani Abraham is ClinTec's Regional Director, Regulatory Affairs and Operations. She has significant experience in both regulatory and ethics submissions in the MENA region, and has worked on multiple multinational trials across a variety of indications and therapeutic areas, including rare diseases.

Prior to joining ClinTec, Rani served as a Clinical Research Associate for global pharma companies and as a Medical Research Coordinator for Dubai Health Authority. She gained her Master's in Pharmacy, majoring in Immunopharmacology and Cancer Chemotherapy, from MAHE University, India.

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