

Iron chelation therapy needed for serum ferritin overloaded patients of beta thalassemia major

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Abstract

The main objective of the current study is to evaluate the level and overload of serum ferritin in multi-transfused beta Thalassemia major patients. There is an earnest need to defend the chelation treatment and to make mindfulness about the results of serum ferritin in the patients beta Thalassemia major.

This is a Cross sectional analytical study performed in Fatimid foundation Hayatabad, Peshawar, Khyber Pakhtunkhwa province of Pakistan. Those patients who has beta thalassemia major are included in this study.

In this study there are total 108 patients in which 54 males and 54 females. The highest mean of serum ferritin level in the category of male was in the age of 12 years were finds 8160.5 ng/mL. Among the female the highest mean of ferritin level was in the age of 17 years were finds 13,349.5 ng/mL.

In this study majority of patient's revealed much high levels of serum ferritin. These levels reveal insufficient chelation. Appropriate chelation of iron load can improve the quality of the life of these patients. The low level of education, Poverty problems, and insufficient health care facility of are the main obstacle in the effective management of ferritin overload in thalassemia patients.

Introduction

Thalassemia is the name of a collection of genetic blood syndromes described by anemia due to greater destruction of red blood cell. Incomplete synthesis of hemoglobin take place in a group of genetic hemolytic anemia's called thalassemia. The

RBCs are small short lived and pale. Two dissimilar proteins, a beta and alpha are the main components of the oxygen-carrying HB (hemoglobin) constituent of the RBCs. The body does not produce sufficient of both of these two proteins if the red blood cells become faulty and cannot transfer enough oxygen. The causing anemia is commonly severe with numerous wellbeing complications like inflamed spleen, bone malformations, weakness and needs consistent life-long transfusion, treatment and medicinal management.^{1,2}

Beta thalassemia

From each parent two globin genes are needed to form beta globin chains, one beta thalassemia will occur if one or both genes are faulty. Severity is depends of on how several genes are altered.^{3,4}

One faulty gene: This is called minor beta thalassemia.

Two faulty genes: depending on temperate or severe symptoms which may sometime called Colley's anemia or thalassemia major is further communal among individuals of Mediterranean heritage. The Prevalence is more in the Maldives Islands, North Africa, and West Asia.³

Signs and symptoms

Beta Thalassemia major has extremes type of thalassemia and indications show up in initial two years of life. Influenced infants fail to flourish, gain weight typically so become gradually pale, irritability, fever, diarrhea, feeding problems, progressive expansion of abdomen is due to splenomegaly and prominence of the cheek bones has a tendency to unclear the base of the nose and to uncover the upper teeth. A trend to a Mongoloid viewpoint of the eyes and the puffiness of the eyelid are common displaying symptoms.⁴ Offspring born with major beta thalassemia are typical at birth, then progress severe anemia throughout the first year of life. Different indicators can comprise bone distortions in face, Shortness of breath, Fatigue, Yellow skin (jaundice) and Growth disappointment.⁵⁻⁸ Thalassemia be able to influence bone marrow to extend, which makes broaden bones that bring about change in bone structure, mainly in skull and the face. Bone marrow extension also makes fragile and thin bones, increasing the possibility of damaged bones.

Iron overload

Thalassemia Individuals can develop an iron burden in their bodies, also from itself with illness or after regular transfusions of blood. Excess iron could effect in harm to heart, liver and the endocrine system that comprises glands produces hormones which

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Contributions: MI and MJK supervised, abstracted, drafting and analyzed data; MU developed the original idea and the protocol; WM, development of the protocol, wrote the manuscript, abstracted data and is guarantor; MW, basic amendment of the original copy for significant scholarly content.

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control progressions in all over the body. The harm is categorized by too much iron deposits. Without suitable iron chelation treatment, nearly all patients that having beta-thalassemia stores possibly deadly iron levels.⁵ In the major beta thalassemia several blood transfusions, improved gastrointestinal iron concentration and ineffective erythropoiesis lead to overload of iron in the body. The Iron overload can be determined by serum ferritin measurement. This Iron overload is a common problem of thalassemia disorders which can lead to the progress of increased mortality and organ impairment. Iron overload weakens immune system, and placing patients at larger risk of illness and infection.⁹⁻¹³

Pathophysiology

Generally, in the mainstream of adult

hemoglobin (HBA) is made of 4 chains of protein, two α and two β globin chains organized into a hetero tetramer. The Patients have faults in either both or β globin protein chain in thalassemia, producing abnormal synthesis of RBCs, the mutation is particular to β globin in sickle-cell illness. The thalassemia's are categorized according to which of the HB molecule chain is affected. α globin chain production is affected usually in α -thalassemia, while β globin chain production is usually affected in the β -thalassemia. α globin chains are coded by 2 closely related genes on chromosome 16 while the β globin chains are coded by a particular gene on chromosome 11.⁹

Distribution

Beta Thalassemia is one of the most regularly hereditary syndromes in the country like Pakistani population, with a prevalence rate of 6%. In Pakistan more than 50,000 Thalassemia patients registered in with many different treatment centers and affiliations focuses everywhere throughout the country.^{10,11}

Serum ferritin

It is a useful checking means for overload of iron in thalassemia major. It has been reported that Ferritin rise with age in non-transfused thalassemia patients particularly when the overload of iron is too much. Ferritin Serum level did not correspond with the any of above factors but a positive correlation with a saturation of serum transferrin was found. The Ferritin level is apparently increase through the rise in number of Blood Transfusions.

In transfused beta thalassemic major patients the iron is specially dispersed to the Reticular Endothelial system, motivating the release of synthesis and release of ferritin to the circulation, that resulting in high levels of serum ferritin.^{14,15} Splenectomy not at all impacts ferritin level, it rises with age in both non-transfused and transfused thalassemic patients particularly when overload of iron is extreme. A greater level of ferritin in a splenectomies patient as compared to an individual with undamaged spleen shows no differences.¹⁴

At the point when the level of serum ferritin ranges at 1000 ng/L (generally after tenth to twelfth transfusion), so then it is point for the most part taken as to start treatment for chelation of iron. The most normally utilized agent for iron chelation is Deferoxamine, a normally happening siderophore delivered and cleaned from microorganism *Streptomyces pious*. An administration of the 40 mg/kg (run 30 to 50 mg/kg) is given as 8 to 10 hour's subcutaneous infusion on at least 5 nights every

week. One particle of chelator bind one molecule of iron shaping a profoundly stable hex dentate complex of iron ferrioxamine at physiologic pH.

An oral agent Deferiprone administered with dose of a 75 mg/kg/day, is also accessible. However, its toxicity and its efficacy profile are undetermined¹⁶ so iron chelation treatment takes a very significant part in the management and supervision of a major thalassemia kid. Ever since in the 1960's the 'gold standard' iron chelator has been (DFO) deferoxamine mesylate, prolonging the life of transfusion dependent thalassemics and improving the quality of life.^{17,18}

However, the requirement for regular parenteral infusions is a clear difficulty, reducing compliance to therapy. Moreover, Regular chelation with DFO is really expensive for patients in the developing countries. A cheap and an orally effective drug with a best caring profile will be an ideal iron chelator, at present yet costly Deferasirox is the orally effective chelator having a practically good care profile, that was permitted by the Food and drug administration for transfusional hemosiderosis in offspring above 2 years of age.¹⁹

In medical practice, chelation starts over and done with the deferoxamine that is given at a 20 mg/kg/d by gentle subcutaneous infusion of over 8 to 12 hours when patients have received 12-to 15 time of transfusions or when the ferritin level is about 1000 ng/mL. Deferasirox once daily is an approved given orally as an iron chelator for the treatment of chronic iron load resultant from blood transfusions. The efficiency of deferasirox in maintaining or reducing body iron has been demonstrated in studies involving large numbers of patients with variation of transfusion dependent anemias.^{20,21}

The basic key iron source in thalassemia is transfused blood so before the starts of chelation therapy the iron intake from that sources must be taken into account. So with in this respect it is also important to consider the symptom for the regular transfusions of blood in which these are included such as the progressively enlarged spleen, inability of the patient to maintain HB level above 7 g/dL, bone deformities, impairment of growth, and Regular transfusions should be sustained in order to keep pre-transfusion HB concentration among 9-9.5g/dL.^{19,22}

Studies have also shown that management with the deferiprone decreases levels of serum ferritin and the concentrations in some but not in the all patients.²³ Also another examination has shown that serum ferritin levels can be decreased and urinary

iron excretion can be increased by raising of the deferiprone dose with above the widely used treatment of the 75 mg/kg body weight for per day and by joining deferiprone treatment with the deferoxamine therapy.²⁴⁻²⁶

The purpose of the present study is to assess the Serum Ferritin overload and the effect of chelation therapy on Multiple Transfused Patients of Beta Thalassemia Major in one of the thalassemia Centre in Pakistan.

Materials and Methods

Study design: Cross sectional analytical study was organized.

Study setting: The study was performed in Fatimid foundation, Hayatabad, District, Peshawar, Khyber Pakhtunkhwa, Province of Pakistan. It is one of the best thalassemic center in Pakistan.

Sampling technique: Study was done through non-probability (convenient Sampling) technique.

Study duration: Almost three months after approval of synopsis.

Data collection procedure: After the permission of medical Superintendent of Fatimid Foundation data has been collect from report donor and recipient attending as per inclusion criteria of study.

Inclusion criteria: Those patients were included in this study who has beta thalassemia major.

Exclusion criteria: Those patients were excluded from study who has thalassemia but they have other types like thalassemia minor, alpha thalassemia and hemophilia.

Sample size selection: Total 108 patients were selected in the study including 54 males and 54 females were screened.

Analysis of serum ferritin level: Serum ferritin level was investigated by enzyme linked immunosorbent assay. Other test performed are hemoglobin electrophoresis, Complete blood count, Total iron binding capacity test and Blood groups.

Data analysis procedures: Data for all ages are collected except <1 years and both sex collected for cross sectional descriptive study.

Results

In the total of a 108 cases of thalassemia major studied in this series, 54 were males and 54 females with a male to female ratio of 1:1. The age at the time of this study ranged between 1 years 5 months and 21 years. The mean age were 12 years. For the data calculation the mean and standard deviation (SD) of serum ferritin and HB

level for both separate male females were finds by ordering the data with the age of 2 to 22 years. The mean of serum ferritin of males was 1444.5, 2727.2, 3337, 3997.67, 6337.8, 8160.5, 7108.5, 7969, 6422, 3826.6, and 7186.4 ng/mL respectively. The highest mean of ferritin level in the category of male was in the age of 12 years were finds 8160.5 ng/mL (Figure 1).

And similarly for females the mean/average of serum ferritin level with the age of between 2, to 22 years were finds to be 1263.25, 2569.25, 2112.8, 5729, 8543.8, 11122.25, 7097.6, 6490.17, 13349.5, 9634.5, and 11625.5 ng/mL respectively. Among the female the highest mean of ferritin level was in the age of 17 years were finds 13349.5ng/mL (Figure 2).

For the hemoglobin the mean of HB level among the male category within the age of 2 to 22 year were finds 4.65, 6.2, 7.13, 7.23, 8.22, 7.55, 6.54, 6.0, 7.1, 6.6, and 8.55g/dL respectively. The highest mean of HB concentration in the category of male was in the age of 22 years were finds 8.55g/dL (Figure 3).

And the mean concentration of hemoglobin in the female among the age of 2 to 22 years were finds 5.72, 7.25, 7.32, 7.03, 7.36, 8.35, 6.62, 7.4, 6.51, 6.55, and 7.4 g/dL. The highest mean of HB concentration in the category of female was in the age of 12 years were finds 8.35g/dL (Figure 4).

For the blood groups in all 108 patients of beta thalassemia among the male category within the age of 2 to 22 years there were total 12A+ve, 20B+ve, 1O+ve, 4AB+ve, and 12O+ve male. Similarly, among the female category between the ages of 2 to 22 years there were total 17A+ve, 1A+ve, 15B+ve, 1B+ve, 7AB+ve and 14O+ve female respectively. In this studies also there were 12 hepatitis C patients founds in all 108 patients of beta thalassemia major. Among them also there were 4 patients who did splenectomy.

Discussion

This study shows that Ferritin increase with age in both non-transfused and transfused patients of thalassemia particularly when the overload of iron is extreme. In thalassemia splenectomy is associated with greater deposition of iron and increased saturation of transferrin iron. The further rise in overload of iron in thalassemia after splenectomy should be accepted in considering the removal of this organ. Also it shows that levels of Ferritin can also rise as a result of harm to the organs, like as the spleen and liver¹¹ but in this study it is found that level of Ferritin is apparently rises with increasing in the number of blood

transfusions that results in iron over load, the extent of iron overload is correlated with the disease severity. In severe thalassemia, overload of iron occurred initial in life also it was independent of multiple blood transfusions.

Other conclusion from the study shows that levels of Ferritin that are too much high can show certain disorders, in which one example is the hemochromatosis, which occurs when our body is absorbs too much of iron. The Other disorders that reason to high levels of iron contain: frequent blood transfusions, type 2 diabetes, hyperthyroidism, leukemia, adult Still's disease, Hodgkin's lymphoma, rheumatoid arthritis, iron poisoning liver disease, such as chronic hepatitis C.¹¹ Perhaps be all the above diseases are the causes of high iron level but in this study it had not found any patients who have high iron levels due the disorders that

contain, type 2 diabetes, Hodgkin's lymphoma, hyperthyroidism, leukemia, adult Still's disease rheumatoid arthritis, that cause high serum ferritin level in thalassemia patient but it is found that not only the above disease are the cause of elevated serum ferritin level in thalassemia patients.

There are many other causes of high elevated serum ferritin in those children individually may be they are not properly chelating it may be due to the unavailability of those chelator facility or it may be their parents lack of knowledge that is they are not getting chelation of iron therapy properly or can be the lack of money and resources for which they not having asses to those expensive therapies in the backwards tribal areas of Khyber Pakhtunkhwa, or developing country, like Pakistan where the free source are less available.

Yet regular frequent blood transfusions

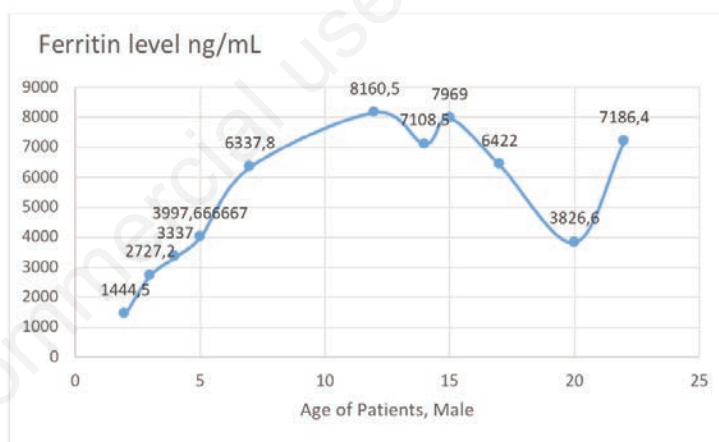


Figure 1. Ferritin (ng/mL) in males patients of beta thalassmia major.

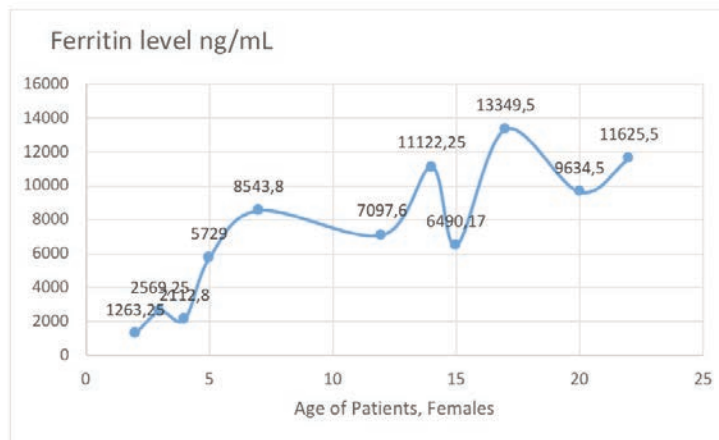


Figure 2. Ferritin (ng/mL) in Females patients of beta thalassmia major.

and not taking chelation properly is the main cause of high serum ferritin but serum ferritin level also increase with the age in both transfused and non-transfused thalassemia patients as in this study it had found that the highest mean of ferritin level in the category of male was in the age of 12 years were finds 8160.5 ng/mL. And among the female the highest mean of ferritin level was in the age of 17 years were finds 13349.5ng/mL.

Another examination found that the basic key iron source is transfused blood in thalassemia so that the intake of iron from that source essential be taken into description before the start of iron chelation therapy. It is significant to consider the symptom for frequent blood transfusions in which includes the progressively enlarged spleen, patient's inability to maintain the level of hemoglobin (HB) above 7 g/dL, bone deformities, growth weakening, and consistent blood transfusions must be sustained in order to retain pre-transfusion concentration of HB among 9-9.5g/dL.^{19,22}

In our conclusion there is a solid need to make awareness amongst the patients and their parents about the outcome, effect, issue, consequences and result of iron burden in their body. High serum ferritin level of major beta thalassemia patients noted in this study supports the basis for consistent follow-up of transfusion dependent patient of Thalassemics with respect to overload of iron to ensure good supervision of iron burden related problems. Appropriate chelation of iron overload can improve quality of the life of these patients.

Majority of the patient's revealed a very high levels of serum ferritin. These levels reveal insufficient chelation and susceptibility to develop iron overload related problems. There is a strong need to rationalize iron chelation therapy, such as at present no chelation, non-availability of infusion pumps, improper techniques of chelator's administration, inadequate chelation, patient's non-affordability to purchase chelators and pumps, improper evaluation of overload of iron and high serum ferritin levels gives an overall of a bleak view.

According to a study which shows that Ferritin level has been reported to rise with age in the non-transfused patients of thalassemia particularly when the overload of iron is too much but a positive correlation with saturation of serum transferrin was found. A higher level of ferritin in a splenectomies patient as compared to people with undamaged spleen shows no differences.¹⁴

The low level of Education, poverty problems, lack of awareness and insufficient facility of health care are the main

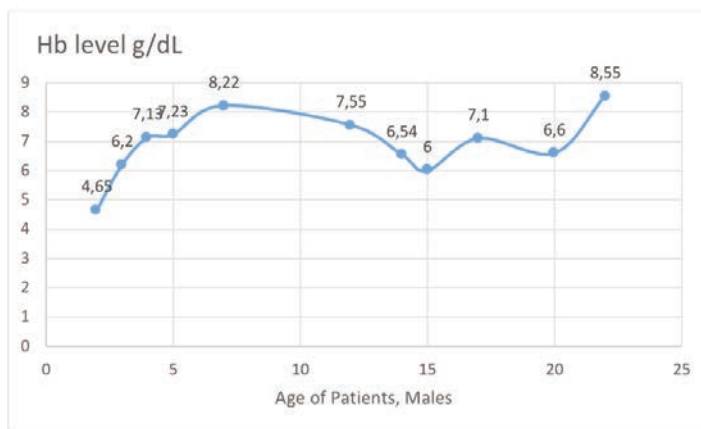


Figure 3. Hb level in male patients of beta thalassemia major.

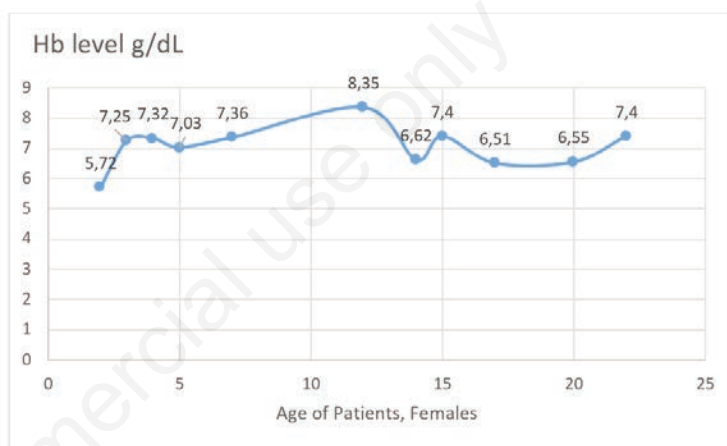


Figure 4. Hb level in female patients of beta thalassemia major.

obstacle in effective management of iron overload in thalassemia patients and that is the main cause of mortality and morbidity in patients of thalassemia major.

References

- Ghodekar SR, Grampurohit ND, Kadam SS, Thorat RM. Thalassemia: A review. *Int J Pharma Res Develop* 2010;2:101-8.
- Ikram N, Hassan K, Younas M, Amanat S. Ferritin levels in patients of beta thalassaemia major. *Int J Pathol* 2004;2:71-4.
- Medline Plus. Thalassemia: MedlinePlus Medical Encyclopedia [Internet]; 2015. Available from: <http://www.nlm.nih.gov/medlineplus/ency/article/000587.html>
- Thalassemia_Types, symptoms, and treatment. Available from: <https://www.medicalnewstoday.com/articles/263489>
- Cappellini MD, Piga A. Current status in iron chelation in hemoglobinopathies. *Curr Mol Med* 2008;8:663-74.
- Vogiatzi MG, Macklin EA, Fung EB, et al. Bone disease in thalassemia: a frequent and still unresolved problem. *J Bone Mineral Res* 2009;24:543-57.
- Mayo Clinic [Internet]. Symptoms and causes - Enlarged spleen (splenomegaly). Available from: <http://www.mayoclinic.org/diseases-conditions/enlarged-spleen/symptoms-causes/dxc-20214722>
- Soliman A, De Sanctis V, Elsedfy H, et al. Growth hormone deficiency in adults with thalassemia: an overview and the I-CET recommendations. *Georgian Med News* 2013;222:79-88.
- Thalassemia syndromes_Lifeline Laboratory. Available from: <https://ypteqadcxjmwldou.quora.com/T>

- HALASSEMIA-SYNDROMES-
Article-By-Lifeline-Laboratory?
ch=1&share=05d7cd5f
10. Thalassaemia Federation of Pakistan. Available from: <http://tfp.org.pk/>
 11. Ferritin Level Blood Test_ Purpose, Procedure, and Results. Available from: <https://www.webmd.com/a-to-z-guides/ferritin-blood-test>
 12. Transfusion hemosiderosis - Wikipedia. Available from: https://en.wikipedia.org/wiki/Transfusion_hemosiderosis
 13. Institute ID. Iron Disorders Institute [Internet]. Tests To Determine Iron Levels; 2009. Available from: <http://www.irondisorders.org/iron-levels-tests>
 14. Shah R, Trehan A, Das R, Marwaha RK. Serum ferritin in thalassemia intermedia. *Indian J Hematol Blood Transf* 2014;30:281-5.
 15. Pakbaz Z, Fischer R, Fung E, et al. Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients. *Pediatr Blood Cancer* 2007;49:329-32.
 16. Hoffbrand AV, Cohen A, Hershko C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood* 2003;102:17-24.
 17. Galanello R. Iron chelation: New therapies - *Semin Hematol* 2001;38:73-6.
 18. Giardina PJ, Grady RW. Chelation therapy in beta-thalassemia: an optimistic update. *Semin Hematol* 2001;38:360-6.
 19. Khan MZ, Khan S, Khan A, et al. Serial serum ferritin levels for monitoring response to iron chelation therapy in patients of beta thalassemia major "Prospective cohort study". *KJMS* 2014;7:245.
 20. Rajish IM, Sumje KW, Butul M, Khan MA. Route of administration of iron chelators-an important factor for patient adherence and acceptance in multi transfused thalassemia major patients. *J Basic Appl Sci Res* 2014;4:61-70.
 21. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β -thalassemia. *Blood* 2006;107:3455-62.
 22. Guideline_Iron chelation treatment - Ithapedia. Available from: <https://thalassemia.com/treatment-chelation.aspx#gsc.tab=0>
 23. Uygun V, Kurtoglu E. Iron-chelation therapy with oral chelators in patients with thalassemia major. *Hematology* 2013;18:50-5.
 24. Galanello R. Deferiprone in the treatment of transfusion-dependent thalassemia: a review and perspective. *Therap Clin Risk Manage* 2007;3:795.
 25. Agarwal MB, Gupte SS, Viswanathan C, et al. Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent thalassaemia: Indian trial. *Br J Haematol* 1992;82:460-6.
 26. Al-Refaie FN, Wonke B, Hoffbrand AV, et al. Efficacy and possible adverse effects of the oral iron chelator 1, 2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major [see comments]. *Blood* 1992;80:593-9.