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Route of administration of Iron Chelators – An Important Factor for patient Adherence and Acceptance in Multi Transfused Thalassemia Major Patients

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ABSTRACT

Background: Beta-thalassemia major resulting in anemia requires lifelong blood transfusions which results in accumulation of tissue iron. The excess iron in the tissues has to be removed by chelation therapy which reduces all iron related complications in the patients. As different iron chelators are available which are administered by different routes, it is important to select a suitable chelator for effective chelation therapy resulting in enhanced patient adherence.
Study design: A retrospective study was done to evaluate patient's adherence and acceptance of deferasirox in comparison to that of deferoxamine. The study is done in Ibrahim Bin Hamad Obaidhallah hospital, RAK, UAE. Case files of patients diagnosed with thalassemia major and on iron chelation therapy during the period 2008 to 2011 were selected and studied. Data on demographics, clinical diagnoses, length of time on chronic transfusions, use of deferoxamine and deferasirox, number of visits for chelation therapy was collected and studied. Occurrence of thalassemia major in different nationalities and different blood group individuals was also observed.
Results: It was observed that there was a 67.85% of decline in patient adherence when the therapy is changed from parenteral to oral in year 2009 but successively in year 2010 and 2011, there is an increase of 7.14% and 58.06% respectively in their compliance and adherence to oral route of administration when compared to parenteral route. Number of visits for blood transfusions progressively increased to 58.33%.
Conclusion: This study demonstrates that oral chelation therapy offers the potential to improve patient compliance and if used in a larger number of patients, would represent a significant advance in the treatment of iron overload resulting in reduction in iron related toxemia.
KEYWORDS: (adherence) AND (iron chelation therapy) AND (oral) AND (parenteral) AND (thalassemia major) Clinical genetics, epidemiology, Hematology (incl blood transfusion), Genetics, Prevention

INTRODUCTION

Hemoglobinopathies are one of the most common disorders observed in people of Mediterranean region. Among various hemoglobinopathies, Beta thalassemia constitutes a major public health problem inthe UAE. During 1989-2004, more than 850 patients have been registered at the Dubai Genetics and Thalassemia Center, UAE.(1) The high degree of consanguinity, especially between the first cousin marriages, resulted in significant number of homozygotes who are on regular blood transfusion and chelation therapy.(1)

Beta thalassemia major is a genetic disorder due to mutated gene in the beta chain of hemoglobin. This disorder requires a patient to undergo lifelong blood transfusion. This repeated blood transfusion will eventually result into accumulation of iron in various major organs of the body including liver, heart, pancreas and kidneys.(2)So there is a possibility that the patient may experience complications to this iron overload due to repeated transfusions and die as a result of the treatment rather than the disease itself. To prevent these complications, patient has to undergo iron chelation therapy after every blood transfusion in order to remove the excess iron in the tissues and to reduce the iron related complications. (2)

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Iron-chelating therapy should be considered in all patients who require long-term red-cell transfusion. Such patients include those with sickle cell disease, myelodysplastic syndromes, thalassemia major, Diamond–Blackfan anemia, aplastic anemia, and other congenital and acquired forms of refractory anemia.[3]

Three chelators, deferoxamine, deferasirox and deferiprone are available having different pharmacokinetic profiles. Individual properties of the chelators should be considered in customizing an individual patient'schelation regimen. [4, 12]Hence it is important to select a suitable chelator for effective chelation therapy, which may result in enhanced patient adherence. This measure increases the effectiveness of treatment and reduces the iron related mortality and morbidity [4]. The more, the compliance to iron chelation therapy, more will be the life expectancy of the patient, with better quality of life and a lesser chance of iron related toxicity due to iron overload.

The effectiveness to therapy is measured by decreased levels of serum ferritin, use of subjective questionnaires like HRQOL [13] or by doing investigations like T2 MRIin these patients. There are many research studies done in the same field which uses well validated tools (SICT, NLI etc) to determine the adherence of patients to chelation therapy. However as this was a subjective measure it has resulted in controversies. Patients who reported to be highly adherent to the therapy failed to show a decreased ferritin levels. There are also some studies that measure the adherence to the chelation therapy by doing investigations like T2 MRI before chelation therapy. These investigations and measures could be done in developed countries with all facilities and resources available.

Treatment with iron chelators has significantly increased the life expectancy of affected individuals into the third to fifth decade [5], while simultaneously decreasing the comorbidities of the disease [6]

A review of published data suggests that compliance with deferoxamine in typical clinical practice is between 60 and 80% [14]. Iron chelation with deferasirox may be beneficial, because it is a once-daily formulation, and it has been shown that regimens requiring fewer pills/tablets [15], or those with a reduced dosing frequency [16], improve compliance.

Self-reported adherence to both deferoxamine and deferasirox were quite high, with slightly higher adherence to the oral chelator (97 vs. 92%). Ninety percent of patients on deferasirox reported at least 90% adherence, compared with 75% of patients on deferoxamine. High adherence in children is likely due to their parental insistence. Lowest adherence from 25 to 35 years possibly reflects conflicting time demands with careers and families. [11]

Another most important factor for the effectiveness of iron chelation therapy is the awareness of the patient regarding the importance of chelation therapy and its consequences that results, if they are not compliant to the treatment. Their family support both psychologically and physically is important for better results.

In less developed countries many people are unaware of the harmful effects of iron overload and think that blood transfusion is the only treatment available for thalassemia patients, so just by increasing the knowledge about it to the patients and their families we can prolong the life of thalassemia patients. All they need is knowledge and the doctors, nurses, students can provide them.

Study Design:

Aim and objectives of the study:

1. To evaluate patient's adherence and acceptance of deferasirox (Oral) Vs deferoxamine (IV/SC)
2. To observe the occurrence of Thalassemia major in different nationalities and different blood group individuals.

MATERIAL AND METHODS:

A retrospective study was carried out in Ibrahim Bin Hamad Obaidhallah Hospital, located in Ras-Al-Khaimah, UAE. Case files of patients diagnosed with beta thalassemia major who was on repeated blood transfusion and getting iron chelation therapy with deferoxamine and deferasirox were collected by gaining the file numbers from the chief hematologist in the hospital. Consent form of the patients were not obtained as it was a retrospective study.

Our inclusion criteria were:

1) Patients diagnosed with Beta Thalassemia Major,
2) Patients receiving repeated blood transfusion upto last 4 years(2008-2011)
3) Patients on iron chelation therapy(IV/oral),
4) Serum Ferritin Levels [7]

Our exclusion criteria were:

1) Patients receiving blood transfusion for diseases other than Beta thalassemia major
2) Other thalassemia groups
3) Patients who stopped taking treatment from the hospital within last four years.

The study proposal was approved by RAK medical and health sciences university Ethics and Research committee. UAE and by the Obaidhallah Hospital Ras-Al-Khaimah, UAE where the research was carried out.

The frequency of patient's hospital visits for parenteral and oral chelation therapy for their iron overload was observed as a measure of effectiveness to therapy. In addition patient's adherence and compliance to therapy was studied by observing the changes in the serum ferritin levels and the no of hospital visits for blood transfusions after the chelation therapy.

Patients were also observed for the prevalence of thalassemia major in different nationalities and different blood group individuals [1]

RESULTS

16 patients during the period 2008 to 2011 were studied, and 5 patients were excluded from the study as they did not satisfy the inclusion criteria. Out of 11 patient's studied (6 were females and 5 males, age between 9 -32 yrs, 4 were UAE nationals, 2 were from Iraq (both brothers), 4 were from Pakistan (3 siblings), 1 patient was from Oman. There were 9 patients with RhD blood group of O positive and 2 patients with RhD blood group of A positive.

s. no.	Age	Gender	Blood group	nationality
1	22	F	O+	UAE
2	16	M	O+	IRAQI
3	22	M	O+	IRAQI
4	25	F	O+	UAE
5	12	F	O+	UAE
6	31	M	O+	UAE
7	21	F	O+	PAKISTANI
8	22	M	O+	PAKISTANI
9	32	M	O+	PAKISTANI
10	25	F	A+	OMAN
11	9	F	A+	PAKISTANI

Figure 1: Variables table(Sample population- number, age, sex, bloodgroup, nationality, serum ferritin)

It is observed that in the year 2008 all patients were on deferoxamine which was administered intravenously (IV) for chelation.

Inspite of the introduction of oral chelator into the market in 2009, hospital visits of patients for IV chelation therapy was 67.85%(n=20) where n=no. of hospital visits.

Number of hospital visits for IV was 20 times more when compared to oral therapy.

But successively in year 2010 and 2011 there was an increase of 7.14%(n=3)and 58.06% (n=10) for oral therapy when compared to the IV therapy.

Number of visits for blood transfusions also progressively increased to 58.33%.

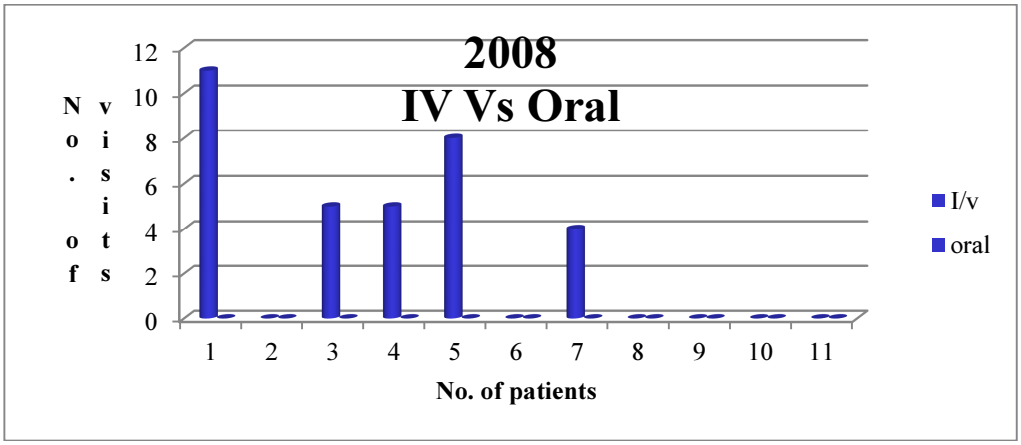

Figure 2: IV Vs Ora1 (in 2008) (Since no oral chelation was introduced, no. of visits for oral chelation was nil.)

In 2008 it was observed that very few patients had come for chelation therapy initially after the blood transfusions.

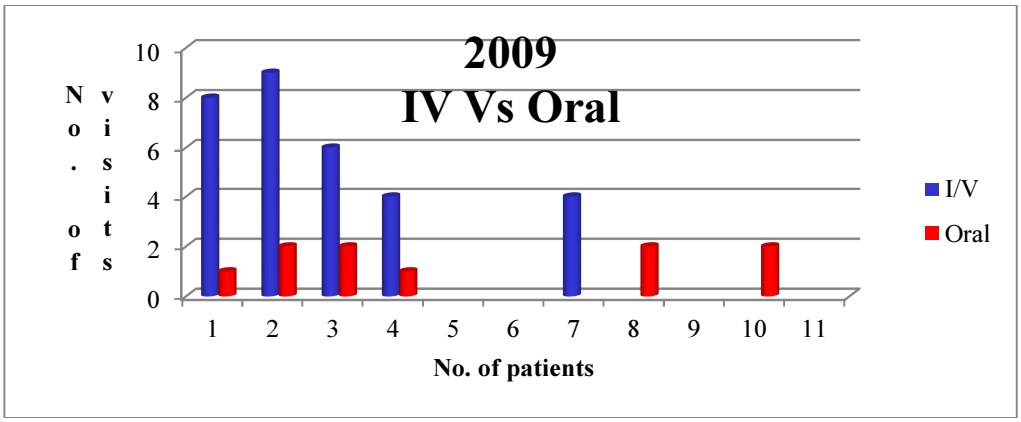

Figure 3: IV Vs Oral (in 2009)(The no. of hospital visits for oral chelation was still less than that for IV chelation.)

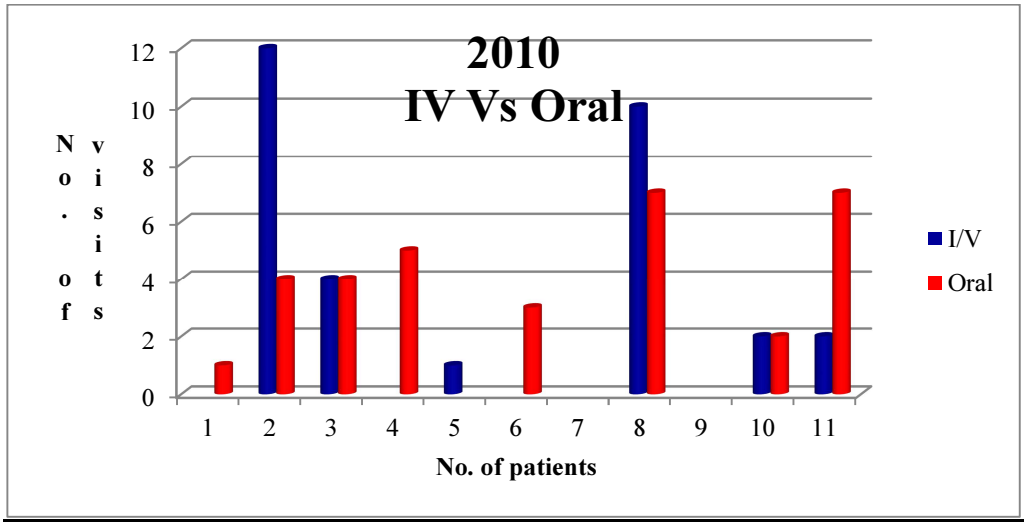

Figure 4: IV Vs Oral (in 2010) (The no. of hospital visits for oral chelation increased because of the availability of the oral drug to a larger number of patients free of cost sponsored by the drug company.)

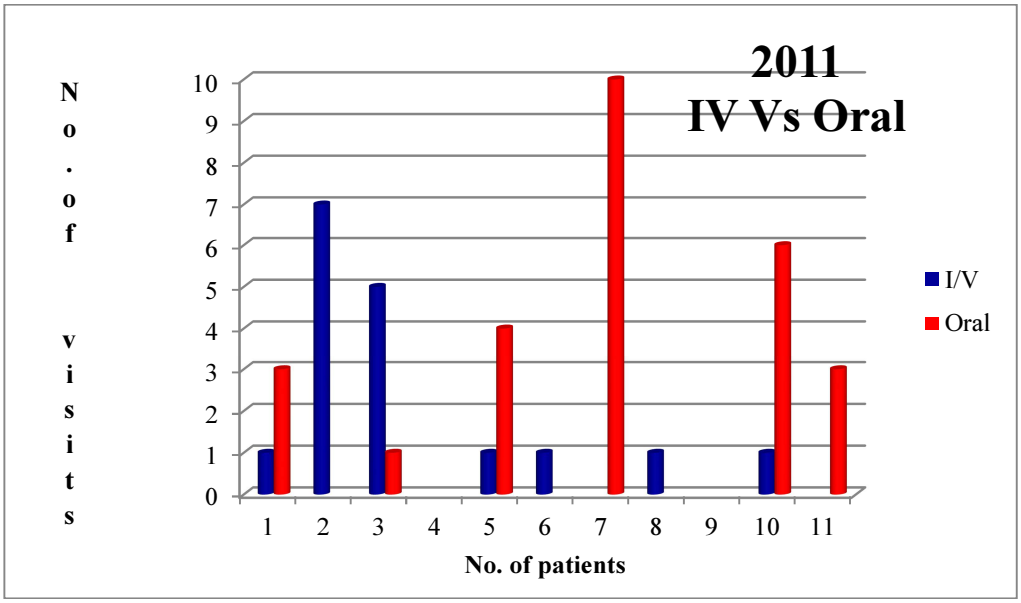

Figure 5: IV Vs Oral (in 2011)

The no. of visits for oral therapy was increased markedly and all the patients were adhering to oral therapy with fewer visits for IV therapy. This suggested improved compliance.

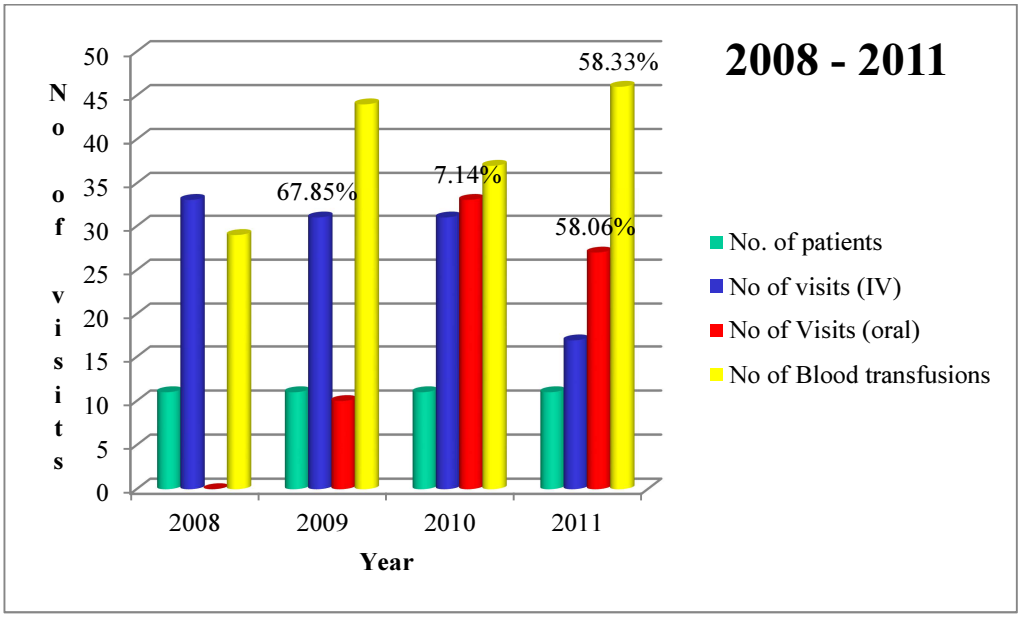

Figure 6: Final result 2008-2011 in percentage

The graph shows no. of patients, no. of visits for Oral therapy and IV therapy, no. of blood transfusions. It shows there is 67.85%: n=20 (increase in visits for IV chelation in 2009, 7.14%:n=3 (increase in visits for oral chelation therapy in 2010), 58.06%:n=10 (increase in visits for oral chelation in 2011)

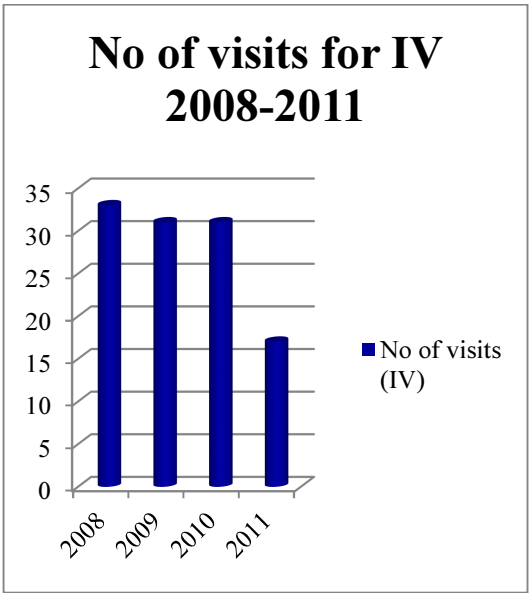

Figure 7: No. of visits for IV chelation (It shows no. of visits for IV chelation is higher in 2008, moderate decrease in 2009, 2010, and markedly decrease in 2011)

Figure 8: No. of visits for oral chelation
(It shows no. of visits were none in 2008, mild increase in 2009, marked increase in 2010, moderate increase in 2011, this is because in 2011 some patients shifted to other hospitals for therapy.)

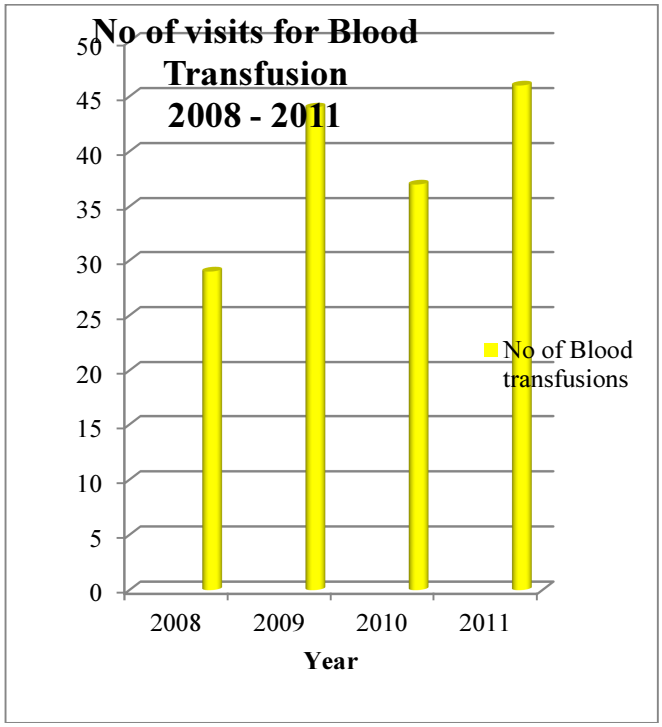

Figure 9: No. of visits for transfusion (It showed increase in no. of visits for transfusion each year which shows that patients are becoming more compliant to therapy)

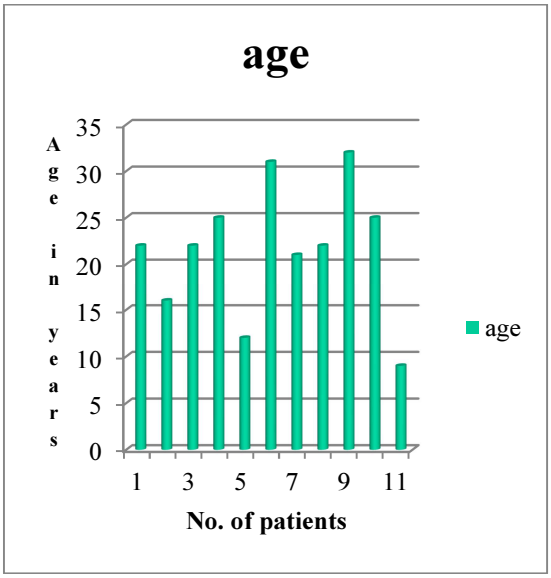

Figure 10: Age chart (This chart shows the ages of the patients in the sample)

The ferritin levels in these patients were abnormally high all the time after transfusion and after iron chelation (though it seemed to reduce after iron chelation but not to the normal values)

All the patients' serum ferritin levels were >2000ng/mL (normal 18-300 ng/ml)

The iron chelation therapy seemed to reduce the ferritin level from >4000ng/mL to up to about 2000ng/mL or more but never did it decrease up to the normal levels (18-300 ng/mL)

Management of iron overload and other associated problems of thalassemia patients were addressed by hospitals of RAK,UAE as follows:

- Iron chelators
- Folic acid
- Blood transfusion(packed RBCs)
- Some antibiotics for infections
- Some receive drugs for acidity (Zantac-Ranitidine) and laxative (Duphalac- lactulose) maybe to reduce the GIT adverse effects of iron chelators.

DISCUSSION

Chronic blood transfusions inevitably lead to iron overload and serious clinical sequelae and patients receiving such transfusions, therefore, require lifelong chelation therapy. Several factors, including the availability of a given chelator and its properties, drug tolerability, transfusional iron burden and the patient's compliance must be considered in the design of optimal, individualized chelation regimens, and all these factors must regularly be reviewed and the chelation modified accordingly.

From our results it was observed that very few patients initially came for the chelation after blood transfusion according to the data of 2008, which could be due to their lack of awareness of the complications of iron overload. Most of the patients were referred from pediatric unit of a Saqr hospital to the Obaidhallah hospital, where repeated blood transfusions were given and as it takes 15 -20 transfusions for the iron load to be manifested, they don't require iron chelation therapy. But after repeated transfusions based on serum ferritin levels, iron chelation becomes mandatory. But as the procedure for administration of deferoxamine was cumbersome and inconvenient and as it required hospital stay for 5 days, patient's compliance decreased.

In 2009, with the introduction of oral chelator, deferasirox and deferiprone, chelation became an outpatient modality. Still very few patients were coming for chelation as limited quantity of drug was available. Many patients had to undergo parenteral chelation. Only those patients who were able to afford it and could pay the cost of the drug were given oral chelation.

There were very few patients who were receiving the oral formulation of drug as a result of introduction of a step wise programme by the drug manufacturers of UAE, to provide the oral formulation of the drug (deferasirox) free of cost only to a limited number of patients who were previously on IV chelation therapy.

In 2010 adherences to oral chelation improved except for two patients who are showing an increase in parenteral chelation in addition to oral therapy. This could be explained on basis of their iron load which was too high and required frequent visits for both types of therapy.

In 2011 there is a small decrease in compliance as few patients preferred to go to other hospitals in different emirates having specialized thalassemia units with improved facilities and improved care given to their satisfaction.

These results suggest that in spite of availability of oral drug in 2009, patient's preferred IV chelation, as the new oral drug was sponsored by the drug manufacturers free of cost initially, only to few number of patients and it was also given to those patients who could afford the cost of the drug.

In later years as the sponsored oral drug was given free of cost to all the patients, their compliance and number of visits to hospital for chelation therapy and for blood transfusions increased resulting in effective treatment of iron overload and leading to more adherence and acceptance to the therapy. As a result of better adherence to chelation therapy, iron overload related complications were also reduced to a greater extent.

Among patients who had previously received deferoxamine and were randomized to deferasirox, 97% said that they preferred deferasirox. The main reasons cited were convenience (37%), less soreness from treatment (25%), less disruption to their day (23%), less disruptive to sleep (6%), and less disruptive to family life (4%).[8]

A variety of factors differentiate the currently available iron chelators. First, pharmacological properties, including the stoichiometry of iron chelation, mode of administration, dosing schedule, plasma half-life, and route of excretion, vary among chelators. Second, drug efficacy is variable, particularly with regard to organ-specific (hepatic, cardiac) iron removal. Third, adverse-effect profiles differ among chelators. These various drug properties ultimately contribute to patient adherence, overall control of iron burden, and the complication profile. Chelation therapy needs to be individualized; the choice of chelator(s) and dosing should be made based on: drug availability and tolerability (including adverse effects), patient preference and ability to adhere to the regimen, ongoing transfusion burden, and trends in organ-specific iron loading.[8]

Adherence to deferoxamine is generally poor and a patient's attitude to adherence can change over time. The availability of oral iron chelators, such as deferiprone and deferasirox, may contribute to improved compliance,

especially among pediatric and adolescent patients in whom compliance is a particular issue. Adherence may also be improved by offering patients greater choice in chelation. [9]

CONCLUSION

Hence this study demonstrates that oral chelation therapy offers the potential to improve patient adherence and compliance to the therapy.

Not Only is Route a factor for better patient acceptance and adherence but the availability and cost effectiveness of the drug also play a major role inpatient's compliance.

Compliance may be improved with additional intensive social and psychological support from their family.

Awareness about the adverse effects of iron overload has to be made to the patients, their family members, and also to the care-givers like the doctors, nurses etc.

Although adherence to chelation therapy is generally poor, the availability of oral iron chelators may help to improve patient compliance. [10]For chronic conditions such as thalassemia major, even when oral chelation therapy is available, support by an integrated team including a clinical psychologist and nurse specialist working with the treatment center is recommended to achieve optimal results [10].

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