

## Sequential Deferoxamine - Deferasirox in Treatment of Major Thalassemia with Iron Overload

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### Abstract

#### Background

Iron overload is a major problem in patients with major thalassemia. An effective and safe iron chelator protocol with high compliance rate plays an important role in treatment of these patients. This study was done to assess the efficacy and safety of the sequential deferoxamine and deferasirox protocol in major thalassemia patients in Khuzestan province, Iran.

#### Material and Method

Sixty two patients were studied aged between 2 to 30 years old. A regimen consisted of 4 days deferasirox followed by 3 days deferoxamine. The duration of trial was 6 months. The efficacy was determined by comparison of ferritin level before and after treatment.

#### Results

Serum ferritin changed from 3590 ng/ml to 2563 ng /ml, which decreased significantly. During study 21% of patients experienced at least one side effect.

#### Conclusion

This is a new regimen with high efficacy, low toxicity and acceptable compliance.

#### Key words

Sequential, Deferoxamine, Deferasirox, Major thalassemia.

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### Introduction

Iron overload is an inevitable problem in major thalassemia patients. Every unit of packed blood cell contains 200 - 250 mg iron (1-2). The body has not active mechanism to excrete iron accumulation. Iron overload can cause tissue damage such as heart failure, liver disease, endocrine disturbances, which could cause eventual death (3-4). There have been established evidences that iron chelator drugs reduce tissue damages and improve life expectancy in these patients (7).

These patients require a continuous iron chelator drugs. The aims of iron chelator therapy in these patients are; firstly, reduce iron burden, secondly, reduce risk of tissue damage especially in specific key organs such as heart and liver, thirdly, improve life survival, fourthly, provide 24-hour protection from the toxic effects of iron such as Labile Plasma Iron, and finally, reduce gap free of iron chelator drugs (8).

High efficacy, low adverse effects, high compliance, and low cost should be added to the aims mentioned above.

In recent years multiple different iron chelators regimens were used, which include monotherapy, combined and alternative sequential regimens (9-13).

This project studied efficacy of alternating sequential Deferasirox (Osveral)/Deferoxamine chelating therapy to decreased serum ferritin.

## Material and Method

This trial was performed on 62 major thalassemia patients, who attended to Research Center for Thalassemia and Hemoglobinopathy-Shafa hospital related to Ahwaz Joundishapur of Medical Science. In these cases 31 were male and 31 female, aged between 6 to 30 years old (mean age 18.5). The duration of treatment was 6 months. For everybody Cell Blood Count (CBC), serum ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BUN, creatinine, urinalysis, visual and auditory examination and echocardiography were tested before treatment and each month after treatment. The efficacy of regimen was estimated by comparison of serum ferritin level before and after treatment. All patients were treated in a mean total daily dose of OSV (Osveh co) 23 mg/kg( range 17.2-30) 4 days a week (Saturday until Tuesday), single dose at least half an hour before breakfast along with Deferoxamine (Novartis pharma co) 50 mg/kg (range 30-55) 12 hours subcutaneously for three next days( Wednesday until Friday). Informed consent was signed by all parents before starting treatment.

After collecting data, statistical analysis was performed by SPSS 16.0.2. Differences were considered significant at  $PV < 0.05$ .

## Results

Out of the 62 patients 7(6.3%) discontinued treatment for medical and personal reasons during first month of treatment. Compliance response was good (95%). Mean serum ferritin concentration declined from 3590 ng/ml (range 1200-7200) to 2563 ng /ml (range 750-5800), which decreased significantly ( $P < 0.005$ ). During trial 13 of patients (21%) experienced at least one general adverse drug reaction (Table1). These events occurred mainly in the first week of therapy and they were mild reaction. Liver enzymes increased in AST and ALT 16% and 18% respectively, which mostly rised two to five times of normal level. Fortunately, AST and ALT decreased after starting treatment in 17% and 27% of patients respectively. .Side effects such as headache, proteinuria, diarrhea, anorexia and abdominal pain were seen in less than 3% of patients. The most significant adverse effect of the protocol was elevated serum creatinine, which occurred in 13 patients. All creatinine rising were in the normal range. Deferoxamine infusion was not associated with abscess at the site of infusion or allergic reactions.

## Discussion

Iron overload is an predictable problem in beta thalassemia patients. Iron chelating agents reduce tissue damages. Monotherapy with Deferoxamine needs an electronic pump for slow infusion over 8-12 hours, 5 to7 nights per week (14). So, most patients refuse this treatment (14-16).

The other iron chelator drug as Deferasirox has a half-life of 3–4 hours, and like DFO is unable to provide 24-hour chelating coverage. Monotherapy have not achieved all therapeutic goals because of short half of these medicines (20-30 minutes for the former and 3-4 hours for the latter) and rapid decline plasma levels (14).

Deferasirox is a effective oral iron chelator with a long half life, which could be used as monotherapy. It could provide constant gap-free chelation coverage with a single daily dose, and has an efficient and selective role on organs such as heart and live (8, 17-18). Deferasirox could produce an acceptable 24 hours iron chelator coverage. However, the efficacy on the high iron overload is questionable. It could not achieve a negative iron balance even with highest recommended dose, which might cause sever side effects. So, none of iron chelator drugs could provide all therapeutic goals in these patients based on the monotherapy approach (19).

Combination therapy first practiced in major thalassemia by Anderson et al. They used combination Deferoxamine / Deferiprone and proposed several potential advantages with this regimen [20]. Medicines with different properties and mechanisms may access different iron pools. The molecule of Deferasirox is small and can easily enter into cells and is able to transfer iron into plasma for Deferoxamine chelation (10-13, 21-26).

This approach of therapy is a flexible regimen ,which would allow the clinicians reduce the nightly Deferoxamine injections and increase the oral doses with high efficacy and low toxicity (20,27-28).

The effectiveness of the alternating use of deferiprone and DFO was initially reported by Aydinok et al in non-controlled clinical study (29).

In present study serum ferritin decreased significantly. This regimen was associated with minimal adverse effect. The major serious side effect of this regimen was creatinine rising which occurred in 21% of patients. All creatinine rising were in normal limits. In monotherapy approach this adverse drug reaction is high [30]. Sequential Deferoxamine / OSV is a new protocol to date with advantages of more time iron chelator coverage, acceptable efficacy and compliance and lower side effects. The alternating use of both chelator is effective in high iron loaded and clinicians could give patients a deferasirox-free period to prevent major side effects. The only disadvantage of this regimen is the gap of the free iron chelator time.

In conclusion, the results of this study showed that sequential therapy of iron chelator drugs has a significant reduction in serum ferritin with considerable compliance and no serious toxicity.

Table I: Side effects of sequential Osveral /deferoxamine regimen

Adverse effect	Frequency	Percent
Rising Creatinine	13	21
Elevated ALT	11	17.7
Elevated AST	10	16
Headache, Skin rash, Abdominal pain, Diarrhea, Anorexia, Proteinuria	1 - 2	1 - 3

## References

- Porter JB. Practical management of iron overload. *Br J Haematol*. 2001;115:239–52.
- Khalifa AS, Sheir S, el Magd LA, El Tayeb H, El Lamie O, Khalifa A, et al. The kidney in beta-thalassemia major. *Acta Haematol* 1985; 74:60
- Ishizaka N, Saito K, Mitani H, Yamazaki L, Sata M, Usui S, et al. Iron overload augments angiotensin II-induced cardiac fibrosis and promotes neointima formation. *Circulation*. 2002.106:1840–6.
- Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complications of beta-thalassemia major in North America. *Blood* 2004;104:34–9.
- Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994.331:567–73.
- Modell B, Khan M, Darlison M. Survival in beta-thalassemia major in the UK: data from the UK Thalassaemia Register. *Lancet* 2000. 355:2051–2.
- Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, et al. Survival in medically treated patients with homozygous beta-thalassemia. *N Engl J Med* 1994.331:574–8.
- Cabantchik ZI, Breuer W, Zanninelli G, Cianciulli P. LPI-labile plasma iron in iron overload. *Best Pract Res Clin Haematol* 2005;182:277–87.
- Nisbet-Brown E, Olivieri NF, Giardina PJ, Grady RW, Neufeld EJ, Séchaud R, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. *Launcet* 2003;361:1597–602
- Hoffbrand AV, Cohen A, Hershako C. Role of deferiprone in chelation therapy for transfusional iron overload. *Blood* 2003;102:17-24.
- Grady RW, Berdoukas V, Rachmilewitz EA. Iron chelation therapy: metabolic aspects of combining deferiprone and deferoxamine. 11th International Conference on Oral Chelation in the Treatment of Thalassaemia Major and Other Diseases. Catania, Italy:2001;74-78.
- Breuer W, Empers MJJ, Pootrakul P. Deferoxamine-chelatable iron, a component of serum non-transfusion bound iron, used for assessing chelation therapy. *Blood* 2001; 97:792-798.
- Link G, Konijn AM, Breuer W, Cabantchik ZI, Hershko C. Exploring the “iron shuttle” hypothesis in chelation therapy: effects of combined deferoxamine and deferiprone treatment in hyper transfused rats with labeled iron stores and in iron loaded rat heart cells in culture. *J Lab Clin Med*. 2001;138:130-138.
- Porter JB. Deferoxamine pharmacokinetics. *Semin Hematol*. 2001;38:63–8.
- Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004;89(10):1187-1193.
- Wonke B. Clinical management of beta-thalassemia major. *Semin Hematol* 2001; 38:350–9.
- Nick H, Acklin P, Lattmann R, Buehlmayr P, Hauffe S, Schupp J, et al. Development of tridentate iron chelators: from desferriethiocin to ICL670. *Curr Med Chem* 2003; 10:1065–76.
- Nick H, Wong A, Acklin P, Faller B, Jin Y, Lattmann R, et al. ICL670A: preclinical profile. *Adv Exp Med Biol* 2002; 509:185-203.
- Cohen AR. New Advances in Iron Chelation Therapy. *Hematology* 2006; 42-47.
- Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ, et al. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet*, 2002.360:516-20.
- Origa R, Bina P, Agus A, Crobu G, Defraia E, Dessì C, et al. Combined therapy with deferiprone and desferrioxamine in thalassemia major. *Haematologica* 2005; 90:1309-14.
- Kattamis A, Ladis V, Berdousi H, Kelekis NL, Alexopoulou E, Papasotiriou I, et al. Iron chelation treatment with combined therapy with deferiprone and deferoxamine: a 12-month trial. *Blood Cells Mol Dis* 2006;36:21-5.
- Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. *Blood*, 2003.102:1583-7.
- Al\_Refaie FN, Hershako C, Hoffbrand A, Kosaryan M, Olivieri NF, Tondury P, et al. Results of long-term deferiprone (L1) therapy: a report by the International Study Group on Oral iron Chelators. *Brit J Haematol*.1995;91:224-9.
- Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V et al. The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. *Br J Haematol*. 2002;118:330-6.

26. Fischer R, Piga A, Harmatz P, Nielsen P. Monitoring long-term efficacy of iron chelation treatment with biomagnetic liver susceptometry. *Ann. Ann N Y Acad Sci.* 2005;1054:350-7.
27. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003; 88:489-96.
28. Pennell DJ, Berdoukas V, Karagiorga M, Ladis V, Piga A, Aessopos A et al. Randomized controlled trial of deferiprone or deferoxamine in  $\beta$ -thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006; 107:3738-44.
29. Aydinok Y, Nisli G, Kavakli K, Coker C, Kantar M, Cetingül N. Sequential use of deferiprone and deferoxamine in primary school children with thalassemia major in Turkey. *Acta Haematologica* 1999; 102:17-21.
30. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with  $\beta$  Thalassemia. *Blood.* 2006;107:3455-3462.